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THE HISTOLOGICAL DIAGNOSIS OF EARLY CERVICAL CARCINOMA

ROBERT MEYER, M.D., Minneapolis, Minnesota

MANY of the problems involved in the diagnosis of early carcinoma of the cervix are not yet satisfactorily settled. It is urgently necessary that criteria be set down which will obviate the subjective approach to the interpretation of histologically demonstrable variations from normal. The only logical control of the correctness of such criteria lies in the observation of the clinical course of the various lesions; such studies have been carried out. It is no longer necessary to postpone a diagnosis until gross tumor is demonstrable. Experience has taught that early histological changes may now be recognized which will certainly lead on to a fatal issue in the absence of treatment. This was at the beginning, and still is, the definition of the malignancy of the tumors we call cancer.

By the same token, histological changes which may resemble those of cancer, but which are benign, may be studied by observation of the clinical course. This has also been done and these criteria recommend themselves for testing and acceptance. Close co-operation between pathologist and clinician may be expected to lead to improvement in the adequacy of the criteria for objective diagnosis.

From the Department of Obstetrics and Gynecology, University of Minnesota.

Charles Sumner Bacon Lecture delivered at the University of Illinois, December 7, 1939.

The histological features of erosion healing of the cervix have been briefly discussed in a previous paper.

LEUCOPLACIA OF THE PORTIO AND CARCINOMA

It is generally recognized that carcinoma of the cervix may arise in the presence of an old leucoplacia. Hinselmann maintains that it usually, or perhaps always, arises from leucoplacia. It must be remembered that white spots are not always leucoplacia but are often harmless and transient thickening of the superficial layers of the epithelium. Philipp followed about 80 cases showing white spots on the cervix over a long period and with repeated examinations, but was unable to demonstrate transitions to carcinoma. The author has seen only 2 cases in which early carcinoma of the portio arose from leucoplacia. These will be described below.

Figure 1 shows a section through a prominent white spot on the portio of a 41 year old woman whose complaint was irregular bleeding. The epithelium on the right, which is the white spot, shows diminution in the number of nuclei and keratinization of the superficial portion. The underlying connective tissue contains more fibrils but fewer nuclei and vessels than the more normal counterpart to the left. This represents, then, a very mild

degree of leucoplacia. Two years after biopsy the portio showed no abnormality.

EARLY CARCINOMA IN OLD LEUCOPLACIA

The first case was that of a 43 year old woman who had had 2 fullterm pregnancies and 1 abortion and complained of leucorrhea for many years. Multiple white spots were found on the portio and a clinical diagnosis of leucoplacia was made. The biopsy excision (Fig. 2) shows a thick superficial cornified layer. The other layers are replaced by carcinoma which has also displaced the connective tissue papillae. The cornified layer, being less readily digestible, has been spared for the most part, though in occasional areas it has been shed. The carcinoma has invaded the connective tissue in many small processes. These can be recognized in Figure 3 as made up of irregularly shaped small cells with deeply stained nuclei. There is no distinct basal layer and the abnormal cells are distributed quite irregularly in the upper layers. The row of irregular, more darkly stained cells at the very surface represents the remains of the stratum granulosum. The cornified layer above this is not reproduced. Near the center may be seen 2 groups of cells with darkly stained smaller nuclei closely packed together. These cells have occupied papillae. In other portions of the material which are not illustrated here, the basement membrane is still intact and sharply separates the epithelium from the connective tissue. In both positions the carcinoma is readily recognized by the atypical character of the nuclei. The carcinoma has, as always, started in the basal portion of the epithelium and invaded upward at the expense of the normal epithelium. The differential diagnosis is not always as simple as in this case, but careful study will serve to distinguish leucoplacia from early carcinoma.

The uterus was removed 3 days after biopsy. The portio as well as the entire collum was thickened (4.5 by 5.5 centimeters). At the margin of the area excised for biopsy examination were 1 elevated small white spot and 2 flat ones. The mucosa of the external surface, as well as that of the cervical canal, was more white than red. The prominent spot proved similar to the biopsy specimen, while the other areas for the most part showed leucoplacia. The carcinoma then was very small and in an early stage. This finding is rare.

In the second case the portio had been treated over a long period of time with corrosives. It was finally amputated because both anterior and posterior lips were covered with white spots. The right side of the portio was somewhat thickened but flat and white. The clinical diagnosis of leucoplacia was confirmed in many areas by microscopic examination. The cornified layer was thin in most places but missing altogether in others. The squamous epithelium was thickened with irregular downgrowths.

In Figure 4 the irregularly thickened epithelium includes a papilla with a dilated vessel. On the left the basal cells are long and irregular. On the right the basal cells are also long and are connected with a small but broad downgrowth, the cells of which have enlarged, irregular shaped, darkly stained nuclei. Nearer the surface the cells are regular and in the upper rows they are flat.

On both sides of a similar epithelial downgrowth in Figure 5, the basal cells of the multilayered squamous epithelium are also irregular and oblong. In the upper layer dilated vessels of the papillae may be seen. This may represent a reaction to treatment. The cells, with the exception of the basal row, are not strikingly changed.

A third downgrowth is seen in another area (Fig. 6). This was well removed from those already described. It is surrounded by 1 or 2 rows of flat darkly stained cells which are connected with the basal cell row of the multilayered epithelium. To the right of this the basal cells are seen covering a papilla and here the basement membrane is quite indistinct. The polygonal cells above the downgrowth are irregular.

All of this is convincing evidence in support of a diagnosis of an early stage of carcinoma originating diffusely in multiple areas. For confirmation, sections were examined until areas were found (Figs. 7 and 8) which show epithelial invasion of lymphatics. In both areas the papillae extend for a considerable distance toward the surface. To the right in

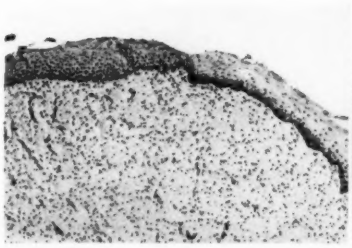

Fig. 1.

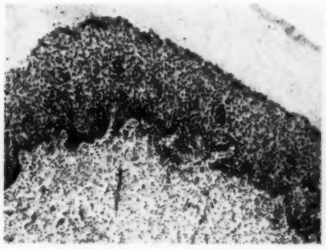

Fig. 2.

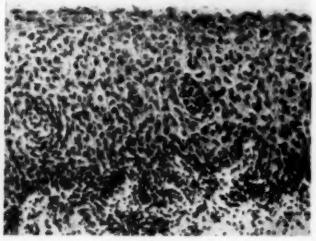

Fig. 3.

Fig. 1. Early leucoplacia of the portio. Low power.
Fig. 2. Early carcinoma on leucoplacia of portio. ×45.
Fig. 3. Higher magnification of same specimen as in Figure 2. ×95.

Figure 7 the papillae are partly included, replaced, and displaced by the irregular downgrowths of the epithelium.

In Figure 8 the epithelium surrounding the large papilla is irregular with defects in the basal membrane. On the left, the epithelium appears normal with the exception of some atypical basal cells. The upper layer of flat cells is the remnant of the benign stage of the leucoplacia. The uppermost cornified layer is missing, presumably as a result of treatment. In the absence of studies of comparable cases it is impossible to determine the part which treatment may have played in the change from leucoplacia to carcinoma.

There is not, on the whole, a remarkable round cell infiltration. It is absent in the areas showing the single downgrowths (Figs. 4, 5, and 6). In Figure 8 it is not striking. In Figure 7 there is a considerable infiltration of lymphocytes adjacent to the multiple downgrowths.

It is important to know that in leucoplacia, carcinoma may arise in multiple areas. Extensive histological investigation is essential under these circumstances.

It is apparent that the first changes always take place in the basal row. The cells and the nuclei become elongated and slender. They are pressed together from side to side as a result of multiplication and are forced to extend in new directions as toward the connective tissue. The basal membrane seems to yield, not only in these areas but also in others. For example, in Figure 6 it seems to yield to the right of the connective tissue papilla. The basal membrane is fading, damaged in all probability by the toxic influence of the carcinoma cells.

In considering the effect of multiplication of the atypical basal cells, it should be remembered that these cells may divide in one of two opposite planes. The plane of the division depends upon the axis of the mitotic spindle. If the plane of division be at a right angle or vertical to the basal membrane, the new cells lie in a plane parallel to this membrane. If the cells divide in a plane parallel to the basal membrane, the tissue becomes multilayered. It appears that oblique layering is usually the result of pressure, and it is not necessary in these circumstances to postulate an oblique position of the axis of the mitotic spindle. In cervical carcinoma, as in other similar conditions, vertical division is the earlier form. On this basis the carcinoma in Case 2 is younger carcinoma than that in Case 1, in spite of the lymphatic invasion in the former. It appears that in the second case, the carcinoma has a tendency to attain a riper form (Figs. 4, 6, and 8) than in the first case.

THE RELATIONSHIP BETWEEN ULCERATION AND EROSION OF THE CERVIX AND CARCINOMA

A consideration of early cervical carcinoma would be incomplete without some attention to the question of its relationship to erosion and erosion healing. A study of very early squamous cell carcinomas leads to the conclusion that they arise always from squamous epithelium and always from the basal cells. In most cases the carcinoma arises at the margin of an old erosion. The author has seen only 1 case of a very small squamous cell

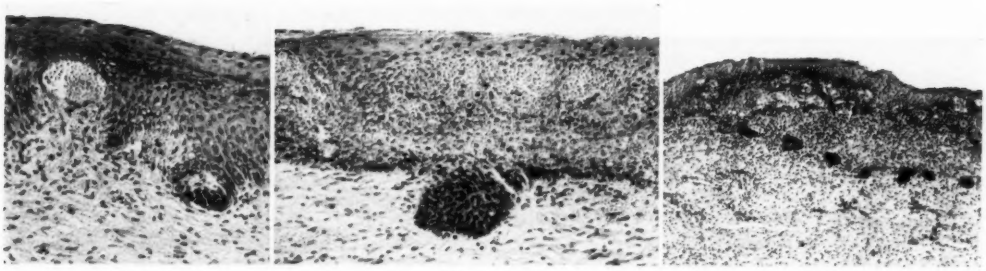

Fig. 4. Fig. 5. Fig. 7.

Fig. 4. Early carcinoma on leucoplacia of the portio. ×115.

Fig. 5. Same case as Figure 4. ×150.

Fig. 7. Same case as Figure 4. ×35.

carcinoma which seemed to arise within an erosion. This is not adequate proof of origin in the erosion area. Such a tumor may have spread to the erosion surface from adjacent surfaces and inflammatory reaction might well have destroyed the tumor in its original site. The tumor might even have arisen from islands of squamous epithelium which are known to remain on occasion intact within the erosion area.

The author has never seen a squamous cell carcinoma of the cervix which did not arise from the surface epithelium. Transitions from benign epidermization to carcinoma are unknown. In order to prove that the newly formed epithelium of the epidermization may be transformed into carcinoma, it would be necessary to show that the latter arises, not on the surface, but deep in an epidermized gland. This has not yet been demonstrated. It obviously cannot be a common occurrence since, with attention focused upon this question for several decades, study of thousands of cases has failed to reveal it.

Similar proof must be demanded to demonstrate the so called metaplasia of mucous epithelium into squamous epithelial carcinoma. Carcinoma must be shown to arise from areas where squamous epithelium and basal cells are absent. Multilayering of mucous cell carcinoma is not comparable and is readily differentiated from squamous cell carcinoma,

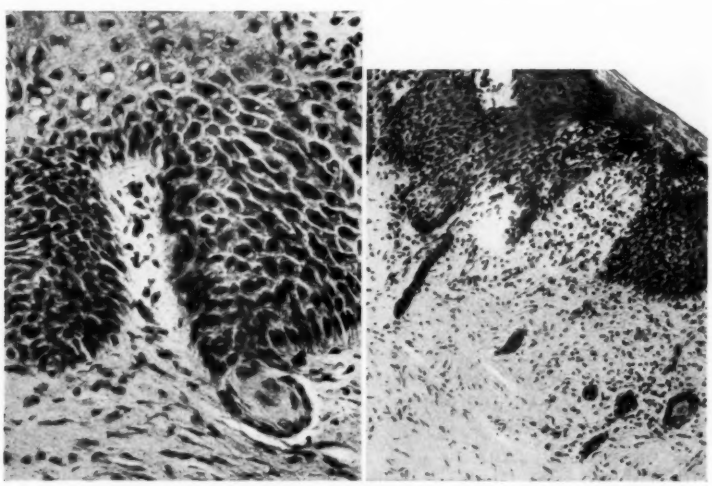

Fig. 6. Same case as Figure 4. ×275.

Fig. 8. Same case as Figure 4. ×110.

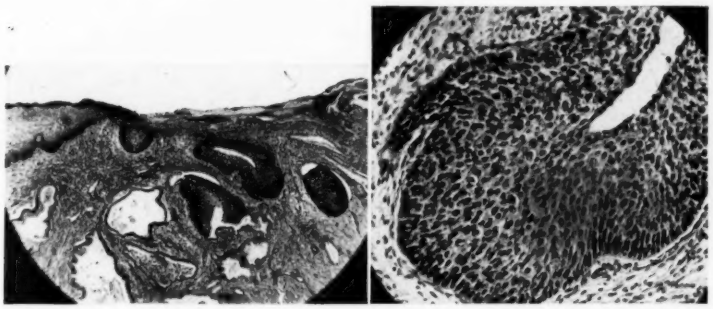

Fig. 9, left. Early carcinoma at the margin of glandular erosion of the portio. Low power.
Fig. 10. A part of Figure 9 under higher power. Membrana propria broken.

particularly in the early stages. Much of the abuse of the term metaplasia will vanish on adequate study of the histogenesis of epidermization and carcinoma.

Polyps, in spite of being covered by ripe squamous epithelium and exposed to irritation, do not become carcinomatous. This is probably due to the fact that there is no older squamous epithelium surrounding the area of epidermization to serve, as in the cervix, for the tissue of origin of the carcinoma. It is true that the squamous epithelium of an old epidermization has the same properties as the original squamous epithelium and might, under certain circumstances, age and give rise to carcinoma. This does not affect the general statement that carcinoma does not arise from active epidermization undergoing proliferation as in erosion healing.

One might conclude, then, that carcinoma and epidermization of erosion are two distinct and unrelated conditions. They both arise from the basal cells of the squamous epithelium at the margin of erosions. But epidermization is a benign restoration and, when completed, approximates the normal. Carcinoma does not arise directly from it.

DIAGNOSIS OF EARLY CARCINOMA IN ASSOCIATION WITH EROSION

The morphological distinctions between epidermization and early carcinoma have been considered in the first part of this paper. Both may spread over the surface and enter glands. For differential diagnostic purposes it is only necessary to keep the characteristics of each condition clearly in mind. The finer cellular histology is not useful at first and, under any circumstances, the usual fixation makes

Fig. 11.

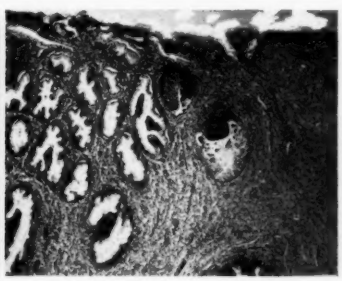

Fig. 12.

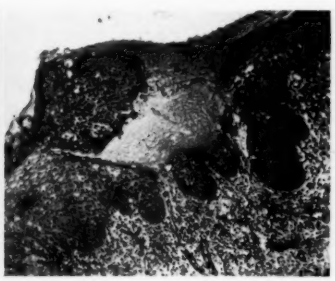

Fig. 13.

Fig. 11. Early carcinoma at the margin of a glandular erosion of the portio. Low power.
Fig. 12. Another instance of early carcinoma at the margin of a glandular erosion of the portio. Low power.
Fig. 13. Early carcinoma on an ulceration of the portio. Low power.

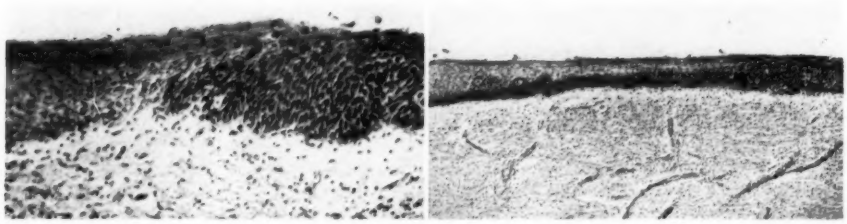

Fig. 14, left. Oblique borderline between early carcinoma and normal epithelium at the surface of the portio. ×115.
Fig. 15. Borderline between early carcinoma and normal epithelium at the surface of the portio. ×45.

demonstration of these features difficult or impossible. The morphological changes which represent the very beginning of malignancy are not known. Mitoses are not usually found in early stages. Abnormal mitotic figures, present in later stages, are not found in beginning carcinoma. Most of the mitotic deviations described in the literature are evidences of cellular regression. Regression is not characteristic of very early carcinoma with the occasional exception of that caused by severe inflammation.

It is characteristic of benign epidermization that, having filled the glands, its demands are satisfied. Even the original shape of the glands is still recognizable. Later, when the epithelium ripens, the glands may become dilated. The proliferation, however, is stopped by pressure. The benign epithelium can invade only along these glands. In contradistinction, the carcinoma uses the glands only as a matter of convenience. It continues its proliferative course, extending and deforming the glands and ultimately breaking through the basal membrane directly to invade the underlying tissue. Direct invasion of the connective tissue may occur in early stages of carcinoma, particularly at the surface as will be described later. Benign epidermization does not extend beyond the basal membrane.

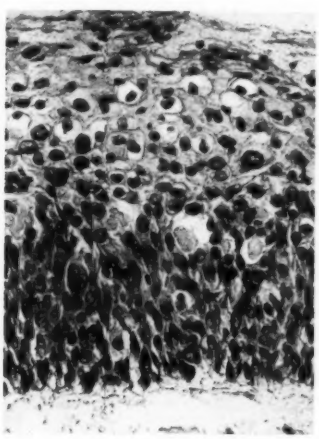

Fig. 16. The basal rows of squamous epithelium are replaced by carcinoma. The carcinoma is also invading the superficial rows of the normal epithelium. ×250.

Figure 9 shows a small carcinoma arising from the basal cells of the normal squamous epithelium at the margin of an erosion. It has invaded and partially filled 3 glands. A small outgrowth of tumor may be seen extending into the connective tissue from the middle gland. This is seen under higher magnification near the left side in Figure 10. A strip of basal cells is forcing its way through the gland basement membrane. The lumen of the gland is not completely filled. The invasion through the basement membrane and into the connective tissue proves, of course, that this is a carcinoma. This fact can be readily recognized as well from the abnormal cell form.

In Figure 11 an early carcinoma may be seen pushing its way into glands, not only beneath the columnar epithelium but in large solid masses which are virtually melting away the original epithelium. Again, the carcinoma arises from the normal squamous epithelium at the margin of a glandular erosion and invades the glands nearest to it. This is repeatedly observed and Figure 12 shows another such case. Not all carcinomas begin here. If there are no glands in the erosion or ulcer, the early carcinoma may directly invade

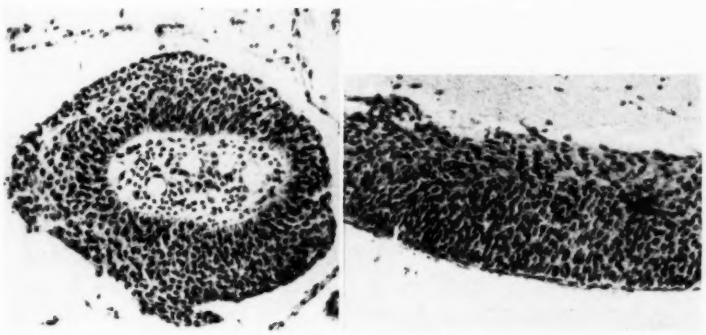

Fig. 17, left. Early carcinoma at the surface in the cervical canal. ×105.
Fig. 18. Superficial carcinoma of the cervical canal. ×140.

the underlying connective tissue. This is apparently accomplished with particular ease when the surface is made up of granulation tissue (Fig. 13). This section also clearly demonstrates the origin of the carcinoma from the basal cells of the normal squamous epithelium. That the epithelium is not destroyed proves that the carcinoma is young.

The early squamous cell carcinoma is usually composed of unripe or middle ripe cells although there are exceptions to this. The carcinoma appears riper at the surface than in the deeper areas. This is due not only to the fact that the deeper portions are younger but also to the effects of exposure of the upper portions to surface conditions.

Carcinoma arising from the epithelium at the margins of an erosion may spread not only over the erosion but away from it, thus destroying the normal epithelium and invading beneath it. This action often proceeds in a typical manner, pushing forward obliquely under the normal squamous epithelium as shown in Figure 14. In this biopsy specimen excised from the portio, the carcinoma is readily recognized on the right. The remnants of the normal squamous epithelium may be seen on the surface while the deeper layers are being destroyed and replaced by the carcinoma.

The basal cell layers of the carcinoma show the greatest rapidity of growth. They first extend laterally, destroying the deeper layer of the normal epithelium. The carcinoma then becomes multilayered by virtue of horizontal cell division and proceeds to destroy the more superficial parts of the normal epithelium. The result is an oblique junction of

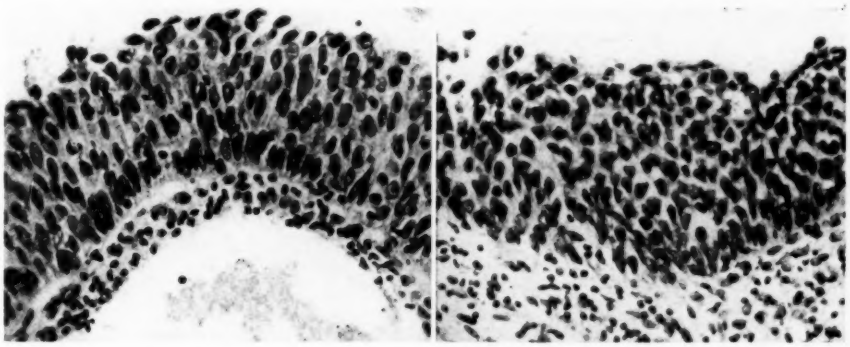

Fig. 19, left. Very early carcinoma of the cervical canal. ×282.
Fig. 20. Same case as Figure 19, 3 months later. ×210.

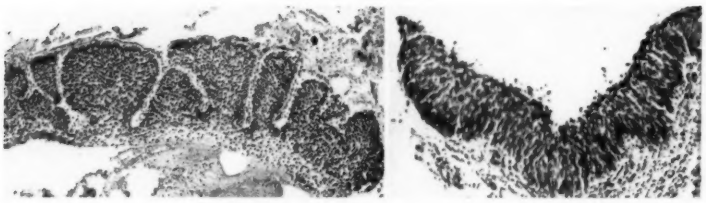

Fig. 21, left. Early carcinoma in cervical canal. ×75.
Fig. 23. Same case as Figures 21 and 22, 10 weeks after Figure 22 was taken. Low power.

tumor and normal tissue with an angle of about 45 degrees. The activity of the carcinoma cells is only one factor in the production of this angular junction. Variations in resistance to growth may play a part. The more dense the cornified upper layers and the less dense the lower layers, as in the presence of round cell infiltration, the greater the tendency to angulation of the line at which tumor and normal tissue meet. The consistency of the connective tissue is also of importance. Figure 15 shows a very small angle between normal epithelium and tumor advancing from right to left. Figures 14 and 15 are taken from the same superficial carcinoma. While the basal membrane in Figure 15 seems to be resistant, it has already been broken through in the area represented by Figure 14.

Figure 16 is taken from the base of a glandular cervical polyp. The patient was 62 years old and showed a carcinoma which had already destroyed a part of the cervical connective tissue and extended over the surface of the polyp. The squamous epithelium covering the polyp has not changed to carcinoma. The latter has extended beneath the benign epithelium and has destroyed the normal basal layers. The borderline between the tumor cells and the remainder of the overlying normal epithelium is not sharp. The carcinoma cells are irregularly shaped with large darkly stained nuclei. They have invaded the remainder of the benign epithelium toward the surface. About half way between basal membrane and surface may be seen several remnants of dead cells. These are not secretion vacuoles but represent the débris remaining after cellular dissolution. The basal membrane is also undergoing dissolution. The fact that normal epithelium covers the carcinoma is only evidence of speedy horizontal extension of the carcinoma at the basal level.

CERVICAL CARCINOMA FOUND IN CURETTAGE MATERIAL

Since the first occasion on which minute pieces of carcinomatous tissue, belonging to

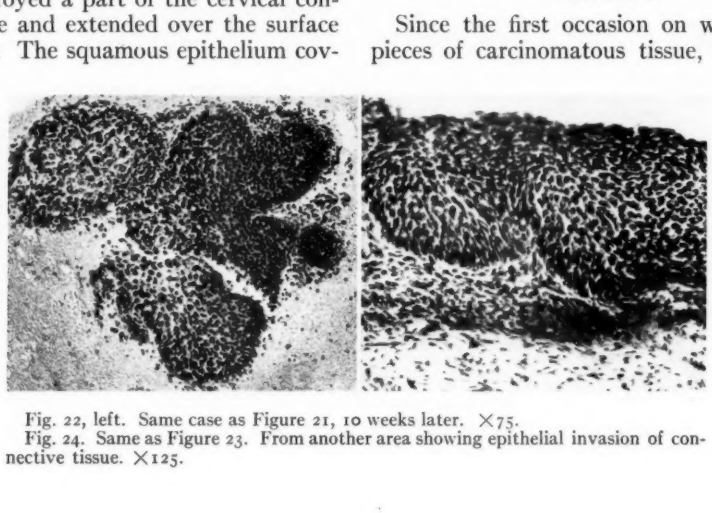

Fig. 22, left. Same case as Figure 21, 10 weeks later. ×75.
Fig. 24. Same as Figure 23. From another area showing epithelial invasion of connective tissue. ×125.

the cervix, were found in curettage material, it has been a routine procedure to cut the blocks of every curettage at multiple levels. As a result of this, a considerable group of very early squamous cell carcinomas were discovered. Garlach, in the author's laboratory, was able to collect a considerable number of these. Descriptions of them will be published in detail in the near future as part of 80 early carcinomas which have been collected over a 3 year period. There is every reason to believe that this is an observation which is of significant importance.

Most of these findings were the result of unintentional curettage of the cervical canal. They were found as small masses and strips of atypical, unripe, multilayered epithelium scattered among the pieces of endometrium. The diagnosis in most cases presented no difficulty.

Most often the carcinoma cells are found in flat strips 5 to 10 millimeters in length. Figure 17, however, shows a section through a small papilla about 5 to 6 millimeters in diameter. There is a delicate stroma with dilated capillaries and lymphocytic infiltration. This stroma seems to be newly formed and it may represent the beginning of a papillomatous form of carcinoma. The patient was 36 years old and had had her last normal menstrual period 3 months before. She had noted vaginal bleeding for only 14 days. The endometrium was in normal secretion phase. The uterus, removed 16 days after curettage, contained a small superficial carcinoma in the cervix. The vaginal surface of the portio was free of carcinoma. The early bleeding may well have been due to the exophytic growth of the tumor.

Figure 18 is from a specimen obtained in a 49 year old woman with hyperplasia of the endometrium. The illustrated small piece of squamous cell carcinoma was found in the curettage material. This combination of endometrial hyperplasia and cervical carcinoma is a rare occurrence. The removed uterus showed a myoma in the fundus. The carcinoma was found in the cervical canal but had remained superficial, perhaps as a result of the exceptionally strong membrana propria.

The 2 following cases present interesting problems since repeated curettages were carried out. The first was a 41 year old woman in whom curettage was done because of irregular bleeding. The endometrium showed nothing of importance. A few small pieces of cervical mucosa (Fig. 19) showed suspicious epithelium. Instead of the normal layering of the epithelium with a single basal cell layer, the epithelium here has a tendency to be similar at all levels. The basal cells do not show the normal clear definition. The nuclei are close together, rich in chromatin, and somewhat irregular in position, shape, and size. It is still more important to note that the cells in the levels above this show similarity to basal cells. They have large nuclei of irregular form, but for the most part they are elongated and have a radial arrangement. They contain less chromatin than the basal row but much more than normal squamous epithelium. The basal membrane is indistinct and invaded by lymphocytes which have infiltrated the underlying connective tissue.

Because the epithelium appeared very suspicious, the cervix was curetted 3 months later and the slightly eroded area on the portio excised. The material is shown in Figure 20. The multilayered epithelial cells have a greater irregularity of form than before and are packed tightly together in an irregular manner. The basal cell layer is absent. The nuclei at all levels are richer in chromatin, and the demarcation between the squamous epithelium and the connective tissue is not as clear as before. The lymphocytic infiltration is not striking. The epithelium has not invaded the connective tissue but is seen elsewhere to have begun to invade the mouth of a gland, melting down the mucous epithelium in the process. The uterus, removed some days later, showed the same epithelium invading the connective tissue in a few areas.

In the second case, curettage was done for irregular bleeding, and a small piece of fairly superficial squamous epithelial cell carcinoma was found. Although the basal membrane seems to be well preserved, there are quite atypical projections (Fig. 21). The epithelial cells of these appear more unripe than

atypical. As the patient was young, the clinician decided to wait. From the second curettage, taken 10 weeks later (Fig. 22), tissue was obtained which showed quite irregularly shaped pieces of squamous epithelium with many atypical nuclei. This is sufficient to justify the diagnosis of carcinoma. Bleeding reappeared and a third curettage was carried out 10 weeks after the second. In the material from the third curettage (Figs. 23 and 24) there is a fairly obvious carcinoma, which is for the most part superficial. In some areas, however, it has broken through the basal membrane and invaded the connective tissue.

In uteri which have been removed after squamous cell carcinoma has been found in the curettage material, the carcinoma was usually superficial and in some cases was entirely above the external os. The region of the external os was most often involved, sometimes with spread to the surrounding areas of the portio. There, as in the cervical canal, the carcinoma had already invaded the connective tissue and, more often, the glands. In only 2 cases were the lymphatics invaded.

In 2 cases no invasion whatever was found and the carcinoma was apparently entirely superficial. In 1 case only 4 or 5 layers of abnormal epithelium were present, but the remains of the original epithelium was being cast off. In 1 case in which a curettage specimen showed apparently superficial carcinoma, metastasis was found in cervical tissue.

In the majority of these cases, the portio presented no suspicious lesions. The endometrium was hyperplastic in 2 cases. With the exception of these 2, the only clinical complaints were some irregularities of the cyclical bleeding. A very few cases presented a history of contact bleeding.

No accurate information can be obtained as to the duration of the lesions. It appears, however, that carcinoma may remain superficial for a few weeks or months. In most of the removed uteri there was invasion of the connective tissue in a few places but this had not advanced very far.

SUMMARY AND CONCLUSIONS

Carcinoma of the cervix can be recognized in its early stages from such material as that obtained at curettage and from the portio. The diagnosis can be made when only superficial epithelium is available for study and without the necessity of observing its relationships to the underlying connective tissue.

It is quite possible to set up objective standards for use in such early tumors. The enlargement of nuclei and their size in relation to the cytoplasm may be measured, and this has been done. The disturbance of nuclear form and size is readily seen. The increase in chromatin content may be compared with that of the normal squamous epithelium. Special stains and photographs demonstrate this readily. The camera may be more sensitive than the eye. Anyone who has developed some facility may make accurate diagnoses. The frequency with which the problem has turned up in curettage material has been surprising.

Theoretical questions have, for the most part, been avoided in this presentation. Into the field of this paper, however, falls the question of the so called precancerous stage or lesion. The author (10) has pointed out that this term may be used in either an obligatory or a facultative sense. Some authors hold that it is an essential concept for clinical usage, while others maintain that the use of the term is dangerous. It is the author's opinion that the epithelial changes in this anatomical region should not be called precancerous.

Recent cancer research has been focused more and more upon the chemical changes within the cells. Koegl has pointed out that all chemical constituents of the cells are continuously renewed. Chronic irritation causes disturbances of the system of cellular ferments so that the cells lose the faculty of incorporating the normal amino acids. A synthesis of abnormal proteins occurs, which progresses slowly until the cells become definitely cancerous. The renewal of the proteins takes at least several months. This has been called the precancerous stage.

The chemical changes within the cells are the result of invisible disturbances. Fischer-Wasels used the term metastructural changes for them. To describe this chemical disturbance stage as precancerous is the same as using this term for morphological changes. To justify the use of the term precancerous, proof

must be available that the chemical and visible changes are capable of both transition to cancer and return to the normal state. At the present time it is not known whether the chemical changes in the cells are inevitably progressive and permanent (obligatorily cancerous) or whether the cells may regain the faculty to produce normal chemical constituents (facultatively cancerous). Only under the latter circumstances would there be logical justification for the use of the term precancer. The interpretation of morphological changes must be considered in the same way.

The morphological changes which have been demonstrated as characteristic of very early cervical cancer are already far advanced in terms of the theoretical onset of the cancerous change in the cell. These have been shown to lead on continuously to more advanced carcinoma. It would seem clear then that these earliest visible morphological changes which are recognized at the present time are those of irreversible carcinoma and should not be described as precancerous. The cases of repeated curettage at intervals, described herein, are of special interest in this regard.

It is important that careful curettage of the cervical canal be adopted as a routine part of uterine curettage.

Objective standards can be accurately applied to the diagnosis of very early squamous cell carcinoma of the cervix.

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THE LIMITATIONS OF THE ROENTGEN DIAGNOSIS OF FRACTURES

ERNEST LACHMAN, M.D., Oklahoma City, Oklahoma

SINCE the advent of x-rays the list of time honored, classical signs of fractures has been increased by one which is at least of equal value. In recent years many courts in this country and abroad have pronounced physicians negligent who failed to use the x-ray in the diagnosis of suspected fractures and have thus marked the radiological approach as superior to all other diagnostic procedures. The erroneous conception has developed that an x-ray report is something objective and indisputable, not open to human fallacies and personal factors of training and knowledge. The fact that the roentgenogram "does not lie," i.e., that it represents objective physical conditions, does not imply that the one who reads it necessarily interprets these physical conditions correctly.

This makes it incumbent on all who utilize the x-ray in the diagnosis of fractures to familiarize themselves with the limitations of roentgenological approach. It is the purpose of this paper to discuss these limitations in connection with the principal points of evidence obtained from the roentgenogram. Considering it the function of radiological procedure (1) to demonstrate the presence or absence of bone fracture, (2) to depict the normal or pathological character of the fractured bone, (3) to disclose the displacement of fragments, and (4) to show the course and progress of healing, then this paper attempts to discuss the limitations of each of these points of x-ray evidence.

A. ERROR OF NEGATIVE ROENTGEN DIAGNOSIS IN PRESENCE OF FRACTURE

Prerequisites for x-ray visibility of fracture. For the sake of this discussion it is assumed that x-rays in each case are used properly under optimal conditions of radiographic technique. Otherwise the field of evidence would be much more restricted. But sometimes, due to the state of the patient, it is neither feasible nor practicable to obtain the proper roentgenograms. Often the decision of the roentgenologist as to the choice of his procedure will represent a compromise between the demand for optimal visualization of the fracture and the caution required in handling a recently injured patient.

It is easy to realize that a fracture may not be apparent on roentgenograms, if, due to the condition of the patient, the customary projections in two vertical planes cannot be utilized. But more relevant to the present discussion is the question: are there fractures which do not show up on the roentgenogram, even if all routine views have been employed? In this connection it is of course necessary to define the meaning of the term "routine or standard views." The technique of x-ray positioning is not static or fixed, it develops with the advancement of roentgenological science, of which it is a part, and with the technical progress of radiographic apparatus. But the following prerequisites for visibility of a fracture should be realized: (1) The dehiscence should at least be of macroscopic dimensions. (2) The x-rays should traverse the bone approximately in the direction of the fracture gap. (3) The fracture should not be obscured by dense, radiopaque bone. (4) In case there is no cleavage at the fracture site, displacement of the fragments should have produced distinct structural or contoural changes. If any one of these conditions is not fulfilled, the fracture will most often be invisible. Further technical factors usually necessary for the demonstration of fractures are: (5) that the fracture line be brought as close to the film as possible, (6) that the exposure be adjusted to the part in question, and (7) that in locations where combined fractures are frequent, all parts be roentgenographed which are potential

From the X-ray Laboratory, Department of Anatomy University of Oklahoma School of Medicine.

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sites of additional bone injuries. Examples based on our own experience or chosen from the literature will illustrate and amplify these statements.

Nonvisualization due to location of fracture in cartilage. Since a fracture is customarily defined as a break in bone or cartilage, it is necessary to point out that cartilaginous fracture cannot be diagnosed from the roentgenogram. This includes fractures extending into the joint cartilage, fractures of the menisci and cartilaginous parts of ribs, and traumatic separations of epiphyses so long as these are not ossified.

Nonvisualization due to minute size of fracture gap. As has been pointed out, the fracture gap must be at least of macroscopic dimensions in order to be visible on the x-ray film. Fissures through the labyrinth of the inner ear may be so fine that they can be demonstrated only microscopically. Then the roentgenogram is of course negative. In metacarpals, metatarsals, and navicular of the hand there occur cracks so minute in width that they cannot be revealed in any projection. In these cases a second roentgenogram after 1 to 3 weeks may demonstrate the fissure after absorption of the damaged trabeculae has led to widening of the gap.

As in the examples just named the microscopic size of the destruction may also be the cause for negative findings in the early stage of Kuemmel's disease of the spinal column. Later, when the damaged trabeculae have been removed, the vertebral body, deprived of the necessary support, collapses (Brailsford). According to this interpretation Kuemmel's disease would be a compression fracture with the fresh injury beyond range of x-ray demonstrability.

The volar-dorsal view, or oblique projections, may depict fractures of the metacarpals and metatarsals otherwise not visible. It seems that insufficient understanding of the limitations of roentgenological procedure is partly responsible for the controversial discussion on the etiology and pathology of "March foot" or "Deutschlaender's disease." With Schinz and Schnek we assume that we are dealing here with invisible fissures of the metatarsals, especially of the second.

Other regions where minute cracks may escape roentgen diagnosis are the tibial condyles and shaft, the patella, the capitulum of the radius. The meshwork of longitudinal tracts of trabeculae in these areas is coarse and wide enough to conceal fine fissures.

Nonvisualization due to insufficient number or wrong choice of projections. One of the essential factors in determining the visibility of fractures is the direction of the x-rays in relation to the fracture line. The dehiscence will be depicted only if the x-rays traverse the bone in the direction of the gap. In most cases the customary projections in two planes vertical to each other will be sufficient to demonstrate the fracture line. Practical experience, as well as consideration of the fundamental laws of projective geometry, prove that one projection is not sufficient to establish presence or absence of a fracture. While it is easy to utilize this knowledge for most of the long bones, in some regions a second projection requires modern technical facilities and skill, often also a certain ability for improvisation. Areas belonging to this group are the shoulder where a second projection has to be insisted upon in case of questionable fracture of the humeral head and neck and of scapula and clavicle.

But in numerous locations even two views may not be sufficient to demonstrate a supposed fracture. Complex or unfavorably located bones or parts of bones, like the sternum, angle of ribs, skull, spinal column including the sacrum, coronoid process of ulna, navicular of hand, os pubis, condylar end of femur, patella, malleolar region of ankle, talus, calcaneus, these often require more than the time-honored two projections. Here the number of fractures overlooked will decrease in direct proportion to the number of projections employed. The underlying principle of these additional projections is usually an axial view, as in the case of the base of the skull, the os pubis, patella, talus and calcaneus, or oblique views as in case of sternum, ribs, spinal column including the sacrum, ankle, navicular of the hand, metacarpals, and metatarsals. In case of ankylosed joints, skull cap, ribs, chip fractures at articular parts of phalanges, atypical positions can often be used to great

advantage. Thus while unintentional deviation from standard positions by careless x-ray technicians may obscure many fractures, discriminate use of nonroutine views by the resourceful roentgenologist will help to reveal fractures which cannot be discerned otherwise. Stereoscopic views in one projection are often not satisfactory for replacing projections from different angles. Of interest is a statistical study which was made by Hunsberger. He demonstrates that in a series of 1035 fractures, in which three or more views were used, 36, or 3.5 per cent, showed up in only a single view.

Nonvisualization of skull fracture. The most complex parts of the skeleton, of course, offer the greatest difficulties in revealing the fracture line. Thus it is not surprising that in skull and spinal column we encounter the greatest number of negative x-ray findings in presence of fracture. In many cases of fresh head injuries it is not in the interest of the patient to take recourse to radiographic procedure at all. In other cases the radiologist will have to be satisfied with few standard views in frontal and sagittal planes, preferably stereoscopic, and desist from special views, such as might be required by the location of the injury. Under these circumstances one should not be surprised to miss a large number of clinically certain fractures. Linear fractures of the base of the skull produce the greatest diagnostic difficulties. Since they can usually be demonstrated only if the x-rays traverse the bone in the direction of the fracture line, it is more or less a matter of chance whether these fractures are depicted or not. Special projections as in the case of the petrous bone improve, of course, the prospects of revealing the dehiscence. Isolated linear fractures of the roof of the orbit and the wall of the pneumatic spaces may also not be revealed on the roentgenogram. In the latter case the opacity of the sinus, as produced by hemorrhage, may give a clue. Fractures of the face and jaw very often require the use of half-axial and oblique positions.

Nonvisualization of vertebral fracture. Fractures of the spinal column are in most cases compression fractures, and are therefore characterized roentgenologically by the absence of a fracture dehiscence. That introduces a new element in the x-ray diagnosis of these injuries, making it incumbent on the roentgenologist to look for contoural or structural changes which are due to displacement of the fragments. Here again the roentgenologist will have to increase the number of so called standard views in order to make full use of the possibilities of x-ray procedure. The time-honored anteroposterior view, even stereoscopically, is certainly not sufficient. Modern technique requires 5 to 7 feet focus-film distance to avoid distortion in the off-center portions of the film. According to Jordan a complete roentgen-analysis of the spine in case of fracture consists of the following exposures: (1) anteroposterior and lateral long distance views of the lumbodorsal spine, with the patient standing or sitting; (2) anteroposterior and lateral long distance views of the cervical spine, with the patient sitting; (3) anteroposterior cone film of the lumbosacral and sacroiliac region; (4) right and left oblique views of the lumbosacral spine showing the intervertebral joints; (5) right and left oblique views of the dorsal spine showing the intervertebral joints in this region. As expensive and time-consuming as this approach may be, it represents the only scientifically correct answer to the problem of roentgen demonstration of spinal injuries. Unfortunately external circumstances and clinical factors may often not permit this extensive procedure. Since the clinical symptom of pain is a very inconclusive means of localizing the area involved, it is wise to include the entire spine in the range of our examination. The best obtainable bone detail is required to reveal minute compression fractures which are characterized by a slight condensation of the spongious texture and minor angulation of the individual vertical axes of the vertebral bodies.

Spot films taken with small cone or rotating anode-tube films are indispensable in these cases. Optimal photographic technique together with appropriate oblique views are necessary for demonstration of injuries to the pedicles, the laminae, and the articular processes. Although not rare, they are not often disclosed in routine anteroposterior or lateral views.

Difficulty of fracture diagnosis in the absence of a fracture gap. Fractures of the vertebral bodies are not the only group of bone injuries characterized by absence of a fracture gap. Calcaneus, talus, lunate, navicular, head and neck of femur and humerus, distal end of radius are other regions where fractures are often revealed only by changes in contour and structure of the bone due to displacement or impaction of fragments. It therefore requires films of optimal quality to disclose the finer textural details.

Difficulty of fracture diagnosis due to superimposition. In some regions the fracture gap, although present, may not be apparent, due to superimposition of other portions of the same bone or of other bones. Fractures of the femoral neck illustrate this well. In external rotation of the leg the femoral neck is foreshortened and obscured by the shadow of the greater trochanter. Thus impacted fractures of the neck may not be diagnosed at all, if the patient is roentgenographed in the position of external rotation, which the fractured leg naturally assumes. Fractures of the vertebral arch may not be visible on anteroposterior view, as they are obscured by the vertebral body. In skull fractures the fracture line is frequently not shown due to superimposition of other portions of the skull. In lateral views of the forearm and leg, parts of the bones which are frequently the site of fracture are projected into the other bone. Thus the head of the radius is obscured partly by the coronoid process of the ulna, and the distal end of the fibula is superimposed over the posterior distal edge of the tibia. If these areas are not carefully checked in other projections, including oblique views, the fracture may be completely overlooked or may be attributed to the wrong bone.

Difficulty of fracture diagnosis due to technical factors. In addition to the principal factors exemplified which decide the visibility of a fracture, other requirements also here listed are closeness of the fractured area to the film and proper exposure. The first may be illustrated by the difficulty encountered in obtaining a clear film of a fractured elbow or knee joint locked in the position of flexion. Here the details of the fracture may not be visualized unless the film is brought close to the flexed joint, either by the use of a curved film or by taking two views in the anteroposterior direction, one for the humeral part of the joint and the other for the radioulnar part (Hunsberger). The same remarks apply to the knee joint.

The importance of adjusting the exposure to the part in question is exemplified by the fact that fractures of the spinous processes of the vertebral column will be overlooked on lateral view, if the exposure is directed toward demonstration of the bodies of the vertebrae.

Nonvisualization in case of multiple fracture. Many fractures are not revealed because the injured part is not included in the x-ray examination. This is especially the case in multiple fractures. The radiologist and clinician are satisfied if one fracture is demonstrated and neglect to study other portions of the skeleton. Thus a fracture of the navicular is not diagnosed in case of accompanying fracture of the radius, a calcaneal fracture is not discerned if combined with a malleolar fracture. A characteristic injury in which one fracture is frequently overlooked is a spiral fracture in the middle or lower third of the tibial shaft combined with a fracture of the fibula below the head. The clinical symptoms of pain and tenderness are often not conclusive means of locating multiple fractures, as is proved in the spinal column. Here isolated fractures may occur at different levels with uninjured vertebrae between them. Frequently pain is referred to the lumbosacral region, when the fracture is actually located in the dorsal vertebrae. Some fractures often occur on both sides of the body, e.g., fractures of calcaneus and radius.

B. ERROR OF POSITIVE ROENTGEN DIAGNOSIS OF FRACTURE IN THE ABSENCE OF FRACTURE

Our discussion so far has shown that in certain regions the chances of overlooking the presence of a fracture are very real. Yet there is even a greater and psychologically more understandable chance of diagnosing a fracture where none is present, an error based on false interpretation of normal or pathological conditions which closely imitate the x-ray appearance of bone injuries. A great number

of these mistakes could be avoided by a thorough knowledge of x-ray anatomy, comprising not only the x-ray appearance of normal structures at various ages, but also the numerous variations of the skeleton which are especially apt to be mistaken for traumatic changes. Other misinterpretations are almost unavoidable at the time of the first diagnosis; they can be cleared up only in due course of time by further clinical and x-ray check-ups. There remains a final group of cases the diagnostic difficulties of which cannot be solved at all with the present state of our knowledge. They touch upon problems which are under scientific investigation or have received conflicting answers in the literature. Although these problems are academic in scope and approach, they are frequently of great practical importance in individual cases when the decision has to be made whether a certain condition is traumatic or developmental in origin. The later discussion on the bipartite navicular, on spondylolisthesis and the Looser zone of transformation will illustrate this.

It will be recalled that for the scope of the present paper it is assumed that the x-rays are utilized under optimal conditions of exposure and positioning, including in many cases a necessary and very helpful comparison with the opposite side. In investigating the sources of diagnostic errors of interpretation it is not intended to enumerate all possible pitfalls of radiological fracture diagnosis. This discussion attempts only to state and demonstrate on illustrative material the principal sources of errors in the roentgen interpretation of fractures, to point out those which are unavoidable and to show means of avoiding the others.

1. *Normal Structures Imitating Fracture*

Since the most characteristic radiological signs of a fracture are the fracture line, or, in absence of a gap, the structural and contoural changes concomitant with the displacement of the fragments, anything simulating a fracture line or the alterations in structure and contour of the bone as produced by a fracture may be mistaken for a fracture. In general, any anatomical condition which leads to interruption of the expected continuity of bone can and has been misinterpreted as a fracture.

Soft structures. Thus, as far as soft structures are concerned, gas bubbles in intestines superimposed over the spinal column or the pelvis, folds of skin and underlying tissues, e.g., in the region of the axilla, buttocks, toes, or the edges of muscles such as the lateral border of the psoas, may produce an apparent discontinuity in the bone over which they are projected, but they can be identified if one follows the questionable line beyond the shadow of the bone.

Epiphyseal lines. Sufficient command of x-ray Anatomy will prevent misinterpretation of the epiphyseal lines as fractures. A further safeguard against this common error is a knowledge of the distinguishing features between epiphyseal and fracture lines. The epiphyseal line is usually of even width throughout, the fracture line is often wider on one end than on the other, the contours of an epiphyseal line are usually smooth and regular, the edges rounded, the contours of a fracture line are rugged and irregular, the edges sharp (Ferguson, and Goldhamer and Swanberg). Yet some younger epiphyseal lines are fairly irregular as e.g., those of the acromion, trochlea of humerus, olecranon, tuber calcanei, but the other characteristics just named still hold true. Often a comparison with the opposite side will show identical findings there and will clear up the question.

The differential diagnostic difficulties are greater when we deal with an old injury where nonunion of the fragments is suspected. Here, as in epiphyseal lines, the contours may be smooth, the edges rounded, but the presence of some reparative signs, as sclerosis and callus formation in case of fracture, ought to afford a possibility of diagnosis (Ferguson).

Due to general endocrine disturbances or some unknown local cause, epiphyseal lines may persist throughout life. If their presence is not suspected and if their general characteristics are disregarded, they are easily mistaken for fracture. A typical example is the os acromiale which occurs at the same site where a fracture might be located.

Variations and anomalies of the skeleton. There is a large group of variations of the skeleton commonly classified under the head-

ing of "accessory bones," that may deceive the beginner and often also mislead the experienced. These supernumerary bones arise from separate centers of ossification representing persistence of "embryonic vestiges which usually disappear" (McGregor). Other accessory bones are due to an abnormal division of usually solitary ossification centers or to failure of centers of ossification to unite. Any one of these abnormal bones may be falsely regarded as of traumatic origin, or at least give rise to diagnostic difficulties. Again in order to avoid these errors their possible sites should be familiar to anyone who interprets x-ray films of bones. Study of their contours and of the outline of the adjacent bones as well as comparison with the opposite side will in most cases clear up their derivation. In recent accident cases control examinations in time intervals will demonstrate traumatic etiology by appearance of reparative signs. But old injuries with pseudarthrosis of the fragments can sometimes not be differentiated from congenital nonunion. In the hand and foot the origin of supernumerary ossicles is frequently an object of heated discussion in medicolegal cases.

Variations in the bones of the hand and foot. A typical example is the divided navicular, which Watkins has called the most troublesome anomaly in the hand. Especially puzzling are cases with recent traumatic history in which the smooth, dense contours of the two fragments forming the bipartite navicular preclude the possibility of recent traumatic origin of the division. Here the differential diagnosis between congenital bipartition and old traumatic nonunion has to be made. Detailed study of the fragment outlines usually does not help, since the contours in old injuries will also be smooth and well defined. There is usually no displacement in either case. The problem of the divided navicular of the hand is typical of the difficulties which may also arise in other regions. The foot is a favored location of supernumerary bones which may occur at the same site as fractures. Their frequency varies from 10 to 12 per cent for the tibiale externum and os trigonum to less than 1 per cent for others. They may be bilateral or unilateral. To complicate the problem still more, supernumerary bones may actually fracture, but may also consist of several bony nuclei as the result of multiple anlage. A good example of this is the bipartite medial sesamoid bone in the first metatarsophalangeal joint. Clinically verified fracture of the same sesamoid has also been described. The characteristics of contour and texture of fractures as compared with the outline and structure of accessory bones should be made use of in the differential diagnosis. Accessory bones may show great variation in size. If they are faint and small, differentiation from chip fracture becomes a difficult problem. According to Ferguson a small bone mass should not be pronounced a fracture fragment unless a corresponding defect has been demonstrated in the bone from which the fragment is supposedly derived.

Variations in the bones of the trunk. In the spinal column there are a number of variations whose differentiation from fractures may cause considerable difficulties. An example of an avoidable yet common error in diagnosis is to mistake the independence of the costal element of the first lumbar vertebra for traumatic separation. The transverse process of the first lumbar vertebra hardly ever shows an isolated fracture. In contrast to this variation the differentiation of an accessory center of the articular process of a vertebra from fracture of the same process is not so easy. Usually the inferior articular processes of the lumbar spine are affected, and the accessory center is separated from the process by a translucent transverse line.

The vertebral abnormality which has probably produced the widest and most controversial discussion is spondylolisthesis. One school considers it a congenital defect of continuity in the interarticular portion of the vertebral arch, based on nonunion of centers of ossification of the fourth or fifth lumbar vertebra. Others have explained the condition as due to an early trauma in the fetus, during parturition, or in infancy. A third group regards spondylolisthesis as acquired in life and produced not by an acute trauma, but by chronic mild injuries or the stress and strain of abnormal weight distribution on a less

resistant area. On the other hand true fracture of the same region might also occur. Meticulous technique and lateral and oblique views are necessary to establish the details which might afford a possibility of differential diagnosis. The final decision between true fracture and congenital malformation often must be left in suspense by the radiologist.

Sutures and vascular grooves. Developmental features in the skull which are likely to be mistaken for fractures are suture lines. On sagittal views the sutures between the temporal squama and adjacent bones are often misinterpreted as fractures. Difficult to identify are atypical suture lines which occur within the frontal or parietal bone and the occiput. These sutures may persist throughout life and imitate fractures. In general the following points should be observed (Goldhamer and Swanberg): the sutures do not extend over more than one bone, while fracture lines may cross over two neighboring bones; fracture lines are usually straight, sutures may be serrated; borders of sutures appear dense as compared with margins of fractures. Traumatic diastasis of sutures is often questionable, since the apparent width of a suture on the roentgenogram depends also on the distance of the suture from the film.

Even more deceiving than suture lines are the vascular markings of the skull. The middle meningeal artery and its branches are the most important of the vessels producing grooves on the inner table of the skull. They are represented on the roentgenogram by transparent lines. Their typical location, their course, their width and lesser degree of transparency may help to differentiate them from fractures. But sometimes, especially if a fissure follows the course of an artery, the diagnosis will be difficult. Not only in the skull have vascular markings been mistaken for fractures. Nutritional vessels in vertebrae, scapula, humerus, radius, ulna, metacarpals and phalanges, and ilium are on record as having been confused with fractures.

2. *Pathological Conditions of the Skeleton Simulating Fracture*

So far in this section of the paper we have discussed normal appearances of the skeleton and congenital variations of the normal simulating the roentgen signs of fracture. But there is a wide range of pathological conditions, the x-ray signs of which can and have been falsely interpreted as fractures. Spondylolisthesis which represents a borderline subject has already been discussed.

Para-articular ossifications. Early x-ray examination will clear up the nature of questionable posttraumatic para-articular ossifications in the neighborhood of the medial condyle of the femur, the greater tubercle of the humerus, the medial epicondyle of the humerus, the lunate. The absence of such shadows on x-ray films immediately after injuries and their later appearance rules out fracture detachments and leaves the alternative diagnoses of heterotopic bone formation developed from small pieces of periosteum freed by trauma, or metaplastic calcification and subsequent ossification of young connective tissue (Crillovich). The diagnostic difficulties are much greater if no early x-ray film exists; then also traumatic detachment of a scale-like fragment of bone has to be considered. Such detachments are especially common on the greater tubercle of the humerus. Here a fourth possibility as the cause of these shadows comes into play, i.e., deposits of calcium in the subacromial and subdeltoid bursae and the tendinous insertions on a nontraumatic and constitutional basis, a disease known as periarthritis humeroscapularis.

Careful attention to Ferguson's rule that in case of traumatic detachment of bone the roentgenologist should look for a defect from which the fragment is derived, together with scrupulous and variable technique, adjusted to each individual case, will help in the differentiation of many of these shadows. But there will remain a number of cases, especially old injuries, in which final identification of these questionable para-articular structures from the roentgenogram is impossible.

Arthritic spurs on calcaneus, olecranon, intercondyloid eminences of the knee joint and vertebral bodies may appear separated from adjacent bones and therefore simulate chip fracture, while in reality they are connected by fibrous tissue which is not visible on the film.

Aseptic necroses. Aseptic subchondral necrosis may produce pictures which closely simulate traumatic separations. While duplication of the bony center for the epiphysis of the tuberositas tibiae is normal, disorganization, fragmentation and necrosis, usually as a result of trauma, represents the condition known as Osgood-Schlatter's disease. It should be differentiated from true avulsion fractures which also occur in this area (Skinner, Ferguson). Similarly Kienboeck's disease of the lunate, osteochondritis of the knee, osteochondritis of the tarsal navicular and fragmentation and necrosis of the capitulum humeri in the elbow joint should not be confused with fracture. Strictly speaking it is a pathological fracture which we encounter in these cases, if we define as pathological fractures breaks in the continuity of bone as the result of some disease of the bone. Thus this problem would be part of the general task of the physician dealing with bone pathology to differentiate between traumatic and pathological interruption of bone continuity. Is it possible in all cases to identify a pathological fracture as such? In other words, will the signs of the accompanying pathological condition which produced the fracture always be demonstrable? As far as the epiphyseal necroses mentioned are concerned the following signs of the underlying pathology will usually facilitate a correct diagnosis: abnormal density, irregularity and disintegration of the fragments, which render impossible a reconstruction of the original shape of the bone from the elements present, often combined with cyst-like bone absorption in the neighborhood.

Pathological fracture mistaken for traumatic fracture. In certain regions of the body the underlying pathology may be obscured due to the compression type of fracture. Thus a spontaneous fracture of a vertebra in senile osteoporosis, which is one of the commonest causes of pathological fracture, may be pronounced traumatic in etiology, since the underlying bone atrophy is not recognized in the collapsed bone. The same holds true for metastatic malignancy of the spine. Case history and x-ray examination of other parts of the spine and of the rest of the skeleton will usually clear up the diagnosis. If a plaster cast is applied to a fracture before an x-ray film is taken, the shadow of the plaster may obscure the accompanying pathology, e.g., a bone cyst as experienced in one of my cases.

Paget's disease of the skeleton and osteogenesis imperfecta may lead to spontaneous fracture without producing on the roentgenogram any evidence of structural changes besides the fracture. But the transverse direction of the fracture gap should suggest the presence of bone pathology (Ferguson). Translucent lines on the convexity of long bones in Paget's disease have found conflicting interpretation. While Schmorl concludes that they are actually fissure fractures of the cortex due to local injury in presence of bone pathology, Brailsford does not believe them to be fractures at all, but interprets them as so-called "Looser's Umbauzonen," i.e., zones of transformation or metaplasia. Looser has described these zones as characterized histologically by lamellar bone resorption and substitution by partly calcified fibrocartilage, fibrous transformation of bone marrow, and marginal periosteal activity. They occur in osteomalacia, late rickets, and ostitis fibrosa cystica, but have also been reported as a disease *sui generis*. Continental authors have found them in the shaft of the tibia, fibula, neck of femur, in the pelvis and calcaneus, especially in young soldiers where there was no acute trauma. Here they are supposed to be due to chronic overloading, "wear and tear fractures" (Reischauer). Roberts and Vogt call them pseudofractures and have encountered them in the upper third of the tibial shaft in children in the absence of acute trauma. The latter authors concede that the exact nature of the disease is not known. Reischauer suggests that march fracture of the metatarsals and spondylolisthesis, also separation of part of the spinous process of the lowest cervical and first thoracic vertebrae as seen in ditch diggers, belong to this group. All in all the pathogenesis and classification of this interesting and complex condition are obscure.

C. LIMITATIONS OF X-RAY PROCEDURE IN EVALUATION OF POSITION OF FRAGMENTS

So far it has been the purpose of this paper to demonstrate the limitations of the x-ray

diagnosis of fractures, pointing out the difficulties and pitfalls of roentgenological evidence. It is likewise necessary, however, to recognize the further limitations of radiographic procedure in regard to information furnished on the position and displacement of fragments.

What has been said, in reference to the diagnosis of fractures, about the necessity of different projections in each case holds even more forcefully in eliciting detailed information on displacement. The literature of recent years gives full account of the need of views from different angles for evaluation of displacement in fractures of the femoral neck, shoulder, patella, talus, calcaneus, spinal column, and others. Stereoscopic views are insufficient to replace additional projections.

In regard to fractures of the femoral neck one can justly say that introduction of the lateral projection has decisively influenced the treatment and prognosis of these injuries. Only complete visualization of the displacement before and during reduction, and careful roentgenological check-up after reduction, will assure success in this treatment. Authorities have stated that omission of the lateral view is probably the most common cause of failure in reduction and nonunion.

The laws of projective geometry make us realize that angulation of fracture fragments toward or away from the plane of the x-ray film leads to wrong evaluation of displacement. Lateral shift of the fragments will be pictured on the x-ray film without distortion only if the displacement has taken place parallel to the x-ray film. The only displacement which can be measured without error on the roentgenogram is the longitudinal, if the proper projection has been chosen (Schinz). Rotation of one fragment upon another is hardest to evaluate by radiographic methods and is only approximately possible if the film includes the joints proximally and distally to the fracture (Schnek).

At sites where parts of a long bone form a conspicuous angle, as between shaft and neck of femur, this angle is of course taken into consideration in reduction of fractures. It is in locations where this angle does not deviate much from 180 degrees that it is often overlooked in correction of displacements. Thus in reduction of fractures of the lower end of the humerus the so called carrying angle between humerus and forearm, which in extension is 10 to 15 degrees, has to be restored. In the same region the anteriorly open angle between the lower articular end of the humerus and the shaft calls for attention. On the lateral roentgenogram of the wrist a plane laid through the joint surface of the lower end of the radius normally forms an angle with the axis of the radius which is less than 90 degrees. The angle is often considerably increased in compression fractures of the lower end of the radius (Skinner). If in correction of the displacement the angle is just reduced to 90 degrees, it will result in considerable restriction of flexion. Similar important angles to be taken into consideration in the reduction of displacements are the angle between tibial shaft and proximal articular portion of the tibia, the calcaneal angle as well as the normal curvatures of femur, radius, ulna, metacarpals, and spinal column. If this normal anatomical relationship of portions of bones is to be appreciated to its proper extent, simple inspection of displacements on roentgenograms is not sufficient. The axes of bones will have to be marked out in the roentgenogram and angles measured in order to obtain the best possible functional results.

Since parts of the fracture line may not be depicted on the x-ray film, a fracture may appear incomplete in cases in which it is actually a complete break. The more frequent application of the lateral view in fractures of the femoral neck has also proved that impactions do not occur as often as thought and that the impression of impaction is produced on the anteroposterior film by overlapping of the fragments.

D. LIMITATIONS OF X-RAY EVIDENCE OF HEALING OF FRACTURE

One of the most important problems in connection with the roentgen symptomatology of fracture is the evidence furnished as to the healing of fractures and the progress and stability of bony union. The following are the x-ray signs commonly used in the evaluation of posttraumatic bone reconstruction: (1) obliteration of the fracture line; (2) amount and

density of the visible callus; (3) formation of bony trabeculae bridging the fracture gap. Taken separately these signs are of questionable value. None of them affords absolute certainty of bone union, nor does their absence prove nonunion.

Thus a fracture line may become invisible, although present, if as in case of pseudarthrosis, exuberant callus is formed, obscuring the cleavage on the roentgenogram, or if, due to the direction of the x-rays, the fracture gap is not visualized. On the other hand clinical consolidation of a fracture may be present and yet the fracture line may still be visible, wholly, or in parts.

Since the amount of callus formation depends on many factors which do not have any bearing on the final re-establishment of bone continuity, it is evident that the quantity of callus visible in the roentgenogram is no criterion for the firmness of bony union. The better the alinement the less callus is formed. Skinner points out that in some fractures without displacement no callus can be demonstrated, and yet healing may be complete. On the other hand excessive and premature movements of the fragments may lead to exuberant callus and pseudarthrosis at the same time. The roentgenological density of callus depends of course on the amount of calcium present in the callus. But the mineral content of callus is not the only factor responsible for its firmness. This depends also, as Haebler and Reiss have shown, on the proportion of colloids and crystalloids in the callus and on the water content of the colloids. The latter two factors are of course not accessible to roentgen determination. This leads to the more elementary question: what part of the healing process of fractures is revealed by x-ray? Ham, Tisdall, and Drake separated the two phases of bone repair, callus formation and calcification, by artificial means in animals whose bones had been fractured, and demonstrated that only the process of mineralization was disclosed by x-ray. Their experiments suggest the possibility that certain cases of apparent meager or retarded union or even nonunion are in reality cases of noncalcified callus. It now is evident why every case of healing fracture presents a roentgenologically latent period of bone repair of from 10 days to 3 or more weeks, and why the palpable callus is often more voluminous than the roentgenogram shows.

The third x-ray sign of re-establishment of bone continuity, i.e., formation of bone trabeculae across the fracture gap, may be deceiving, since it may be simulated by a slight change in the angle under which the film is taken. In this case the bone texture in front of or behind the fracture gap may apparently be traced across the fracture gap, although in reality the fracture line has not been obliterated. Portable equipment is usually not satisfactory in eliciting the signs of bony union. It is especially in the femoral neck that the x-ray evidence of bony union has been unreliable. Skinner, and Garland and Hill warn against evaluation of films of fractures in plaster casts for evidence of healing. Even more difficult is the roentgenological evaluation of bone repair in fractures of the spinal column. Neither anteroposterior nor lateral views afford roentgenograms which show sufficient detail to depict the extent of the callus formation.

For correct appraisal of the final result of a fracture, it is necessary to differentiate sharply between delayed union and pseudarthrosis. The diagnosis of pseudarthrosis requires positive evidence expressed by the following x-ray signs: rounding-off or tapering and sclerosis of adjacent ends of bone fragments; visible diastasis between the fragments; retrogressive processes in the callus (Pfab).

Other signs sometimes used to verify bone repair are: maintenance of relative position of fragments after a trial of weight bearing; maintenance of relative position of fragments demonstrated on roentgenograms taken in different positions of the articulating parts (Lewis). But, as conceded by Garland and Hill, internal fixation by nail in fractures of the femoral neck may maintain the alinement of fragments and permit weight bearing without bony union having taken place.

Summarizing this discussion on the value of x-ray examinations for the appraisal of bony repair, it can be concluded that x-ray evidence of bony union has to be used with great reservation and only in conjunction with other clinical findings.

The problem of demonstration of the process of fracture repair on the roentgenogram is important also from the medicolegal point of view. In this connection the following questions may arise: Can the x-ray signs of fracture disappear so completely that occurrence of a fracture in the past history of the patient cannot be established from the film? The answer is in the affirmative. Reconstruction of the bony pattern may be so perfect that no trace of the fracture is left in the roentgenogram. Also of medicolegal importance is the question arising in case the presence of an old fracture is disclosed on the film, whether the approximate date of the injury can be established. *A priori* one would assume that the gradual disappearance of the fracture line and the consecutive reparative and retrogressive changes in the callus would afford some means of determining the time of fracture. In general it can be said that the younger the fracture, i.e., the more active the evolutionary changes in bone repair, the closer one will come in estimating the correct date of the fracture. Rentsch points out that up to one year after the injury it is possible to determine approximately the date of fracture from the film. But even here great variations occur, depending on the location of the fracture, the displacement of the fragments, the age of the patient, the type of treatment, constitutional factors etc. After 1 year's duration it is almost impossible to arrive at the date of the fracture from study of the roentgenogram. Leaving aside fractures of the skull, the roentgen picture of the average fracture will become stationary after that period so that no further changes might be expected.

CONCLUSIONS

In the light of the described limitations and in order to make full use of the diagnostic possibilities of the roentgen rays, realization of the following facts is necessary.

1. The x-ray examination has to be preceded and checked by detailed physical examination which, in evaluation of fracture repair, is equal or superior to x-ray studies.

2. More complex skeletal structures require modern shockproof and powerful equipment and complete command of the technique of positioning. The latter includes the utilization of oblique, axial, and long distance views, and, if necessary, of atypical improvised projections. The best and most comprehensive technique is especially needed in evaluation of displacements.

3. For the physican dealing with traumatic bone surgery it is necessary to master the laws of x-ray physics, especially of projective geometry. Further requirements are a thorough knowledge of x-ray anatomy, comprising not only the x-ray appearance of normal structures at various ages, but also of the numerous variations of the skeleton. Knowledge of normal anatomical angles and determination of the normal anatomical relationship of portions of individual bones is part of the field of x-ray anatomy. In order to distinguish between traumatic and pathological interruption of bone continuity one must also be familiar with the x-ray symptomatology of bone diseases.

4. X-ray examination immediately after a doubtful injury may remove otherwise unavoidable diagnostic difficulties and will put medicolegal testimony on more solid ground. It will be especially helpful in the differentiation between fractures and accessory bones and in the identification of posttraumatic para-articular ossifications. In case of older bone injuries of a questionable nature also in check-up on bone repair, serial x-ray studies in time intervals will clear up many diagnostic problems.

5. The confines of the field of roentgen diagnosis of fracture are not irremovably fixed. They change with the progress in roentgenological science and with the technical development of radiographic apparatus. The limitations of today denote the advances of tomorrow.

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THE TREATMENT OF PERSISTENT RECURRENT BASAL CELL CARCINOMA OF THE FACE

FORREST YOUNG, M.D., Rochester, New York

BASAL cell carcinoma occurs most frequently on areas of the body not protected by clothing, hence its most frequent location is on the face. It is a slow growing tumor which remains local. Since the lesions are on the surface of the body and in a place constantly inspected, they are usually recognized and treated as early as any carcinoma of the body. This combination of circumstances, early recognition, easy access of therapy, and slow growth without tendency to distant metastases, moreover, makes this one of the carcinomas most frequently cured.

In spite of these facts a small percentage of these growths recur. It can be fairly said that recurrence of a basal cell carcinoma usually means inadequate initial treatment. Whether excision, irradiation, local destruction with the cautery or electrocoagulation, are used originally makes little difference. The choice of the method is not so important as the skill and thoroughness with which it is applied. These modes of therapy are all satisfactory if used sufficiently radically on adequate areas.

Unfortunately, primary treatment is not always adequate. There are probably a number of reasons for this. These early lesions are regarded by many as having very little potential danger. It is well known that a high percentage of cures can be obtained, and there is a certain squeamishness in most of us which causes hesitation in destroying tissue to the point where disfigurement results. These considerations and, in some instances, ignorance of the principles involved in efficiently using the therapeutic agent chosen, tend to promote inadequate initial treatment.

The tendency to regard these lesions lightly is unfortunate, for the initial opportunity is the golden one. Once a basal cell carcinoma recurs it is no longer a simple problem. However, it is often regarded so, and far too frequently a second small excision or a second course of irradiation is prescribed for the patient, following which the growth recurs rather promptly.

It is my opinion that once a basal cell carcinoma of the face has become persistent, cure can oftentimes be effected only by destroying tissue of such magnitude that disfigurement results. It is much better to accept this viewpoint and turn one's attention to ways in which to minimize or repair the damage necessary for cure than to continue temporizing.

Again, it matters little in what way this wide destruction of the growth is accomplished so long as it is adequate. However, if it is obvious that reconstruction will be necessary, it is technically easier to effect repair if the lesion is surgically excised rather than destroyed by radiation. Following irradiation there is a certain amount of devitalization of tissue adjacent to the destroyed area which makes it difficult to get new tissue to grow satisfactorily when transferred. Then, too, the process of treatment is longer, with its attendant economic loss. Moreover, irradiation alone of a growth once or twice recurrent following previous irradiation is not efficient. In such instances irradiation should be used only as a cautery would be used prior to surgical excision and repair. The cautery, or electrocoagulation, is a preferable agent for this purpose since it leaves tissue around the destroyed area in a more normal state. Cautery destruction of tissue prior to surgical excision is needed only occasionally. It is most useful in removing a sloughing or ulcerated and infected tumor, in order to get a field for surgical excision which is not heavily infected.

I have gradually come to the conclusion that it is much safer to eradicate these recurrent, persistent growths and repair immediately than is commonly thought.

This viewpoint is not in accord with the generally accepted teaching that the defect left should be kept open for inspection for 12 to 18 months, and, if recurrence does not take place in this period of time, repair should be carried out. In primary surgical removal of certain carcinomas about the face, this rule of leaving the defect open for observation has never been adhered to. For example, in carcinoma of the lip, even when extensive, immediate repair is usually done. The same holds true for small lesions about the face when closure by suture is possible. In general it might be said that, when the growth is deeply located, as for instance in the antrum, when bone or cartilage is involved, and particularly when the lesion is extensive or recurrent following previous irradiation or surgical excision, this belief that the wound should not be repaired at once has been the one usually held. I have a suspicion that subconscious doubt as to how to effect repair often enters into the decision to leave the wound open.

I agree that in primary surgical extirpations of certain tumors about the face, repair should be delayed. In general, deep invasive growths the complete eradication of which is doubtful, should not be repaired until one is certain that recurrence is not probable. However, large surface areas of growth should not be a deterrent to immediate repair if the surgeon has no lurking doubt in his mind that some cancer may have been left behind.

When a patient presents a persistent recurrent carcinoma of the face, the treatment should be radical surgery. Our plan at present is to examine the area carefully, determining as accurately as possible the surface involvement and estimating the depth of the tumor in its central or most active portion. In such a survey it must be remembered that recurrent basal cell carcinomas often extend outward under perfectly normal appearing skin. There is a characteristic thickened, slightly indurated feel to these, and the eradication must extend well outside this zone. If the growth is thought to be extending into bone, x-ray films of the region should be studied. Biopsy is useful in estimating the degree of malignancy. If the growth has an active fungating, necrotic center it may at times be advisable to eradicate this area either with the cautery or by heavy irradiation limited to the central portion of the tumor. This, however, is done with the patient understanding that this is merely a preliminary step in the treatment and that radical surgery and repair will accompany or follow. This central destruction is done both to remove gross tumor and to produce a cleaner area for excision. If the cautery is used it often is combined with the first step of preparing material for repair.

During this examination one can draw a line about the tumor indicating its extent and about this another line, allowing a margin of one-half to one inch of good tissue. Such a procedure allows one to determine whether there is a possibility of primary closure or whether tissue must be brought from elsewhere to effect restoration. In no way must the margin of good tissue be sacrificed in order to make repair easier. It is better to err in removing too much rather than too little good along with the bad.

If the decision is made that tissue must be transplanted to restore that which must be removed, then plans are made *in advance* to meet this need.

This is a perfectly feasible method of handling persistent recurrent carcinoma of the face since in most instances the growth is restrained somewhat by the fibrous reaction to previous irradiation. Thus one has usually a demarcation of good tissue and tumor. If tissue is prepared for repair prior to excision of the growth, then at the time of excision the fresh wound can be repaired immediately. This prevents the necessity of long continued care of a large open lesion with its attendant economic loss. In some instances it may be possible to remove the tumor and carry out repair in one step. In the majority it will be necessary to prepare either tube grafts, delayed flaps, or a combination of the two prior to excision. These preliminary steps can often be carried out under local anesthesia without hospitalization. As soon as the condition of the tissue for repair is satisfactory, the patient is admitted to the hospital and radical excision of the growth and repair are carried out in one step. Some 4 to 6 weeks later, if a

pedicled transfer has been used, the pedicle is removed under local anesthesia without hospital stay.

This plan in the majority of instances entails one major operation with hospitalization and, usually, three minor steps without hospital stay. It enables one to remove the growth thoroughly without prolonged hospitalization or great economic loss due to inability to remain at work. Moreover, it offers a fairly high percentage of long arrests of the tumor which in these persistent carcinomas is impossible to obtain by any other means now at our disposal.

CONCLUSIONS

The majority of basal cell carcinomas are at present treated initially by irradiation. This is an efficient method; it does not entail hospital expense, in many instances the patient can continue at work, and there is minimal disfigurement. However, once recurrence occurs following adequate primary irradiation or after presumably inadequate irradiation repeated on numerous occasions, then radical surgical extirpation should be done.

In most instances these recurrent lesions can be satisfactorily eradicated by generously estimating in advance the amount of tissue which must be removed; if necessary, preparing the tissue for reconstruction beforehand, then radically removing the lesion surgically, and at the same time repairing the loss occasioned.

CASE 1. M. C., S. M. H. No. 85,607. I first saw this 42-year old, white, married woman, a doctor's secretary, on October 26, 1937. She wanted advice about a lesion in the skin of the left temporal region. About 7 years before, at the age of 35, a small scaly lesion had appeared in this location. It had been treated by surgical diathermy and afterward by x-ray, the amount unknown. About 2 years later the scar became raised and indurated and a scale would form repeatedly over it. At this time, February, 1934, treatment of 100 milligram hours of radium in contact with 1 millimeter of platinum filtration was given. In November, 1936, about 2½ years later, the growth recurred. On this occasion she received 100 milligram hours with 1 millimeter of platinum filtration at 1 centimeter distance. In 11 months there was a recurrence and on this occasion, October 26, 1937, I saw her for the first time.

This young woman then had had treatment by surgical diathermy and x-ray with recurrence, contact radium 100 milligram hours with recurrence, and then 100 milligram hours radium at 1 centimeter distance with recurrence; these 3 recurrences being during a period of, roughly, 7 years. During these years as far as I could determine a biopsy had never been done.

On examination in October, 1937, there was found a small white scar in the left temporal region about 1 centimeter in diameter. Anterior and inferior to this there was an irregular induration of the skin for a distance of 2 centimeters. In one area there was a slight crusting of the skin.

The history and character of the lesion was compatible with a basal cell epithelioma. In view of the repeated recurrences following irradiation it seemed that wide surgical removal and repair was the best treatment, and this was advised.

Accordingly, on November 12, 1937, the area was excised under local anesthesia, allowing 1 centimeter of good tissue around the zone of infiltration, going deeply under the growth and lifting it out in one piece. A full thickness, free graft of skin from the abdomen was applied immediately. This took completely. Microscopic examination showed the lesion to be a basal cell epithelioma. She has been followed now for 2½ years, and as yet there is no evidence of recurrence. Her only complaint is that the graft is whiter than the surrounding skin. This could have been prevented by taking the graft from the postauricular regions or neck. However, with the aid of dressing her hair judiciously and using cosmetics, the blemish is not too unsightly.

CASE 2. D. M., S. M. H. No. 102,056. This 60-year old Italian laborer was first admitted to the clinic of the Strong Memorial Hospital on April 30, 1935. He complained of an ulceration of the right side of the nose which had first started about 15 years before. At first the lesion was slightly raised, dry and rough, and bled occasionally. About 4 years prior to admission to the clinic, the area was excised by his physician and he was given a few x-ray treatments. He had no trouble for about 18 months. The lesion then re-appeared, ulcerated, and grew rapidly to about twice its original size. He returned to his physician and had one x-ray treatment but did not continue them because of expense. The ulceration continued to progress during the next 2½ years without treatment. He then entered the clinic.

At that time an ulceration was present which had destroyed the skin and alar cartilages of the right side of the nose. The septum was exposed, and around the ulcer there was a zone of inflammatory tissue which bled easily. There was considerable purulent exudate.

General physical examination revealed a hypertension of 190–100, a cataract of the right eye, general arteriosclerosis, benign prostatic hypertrophy, and a 4 plus Wassermann.

The right side of the nose was treated by giving a total of 1100 r x-ray divided into 3 doses on three successive days. He was then followed in the outpatient department until June, 1936. During this

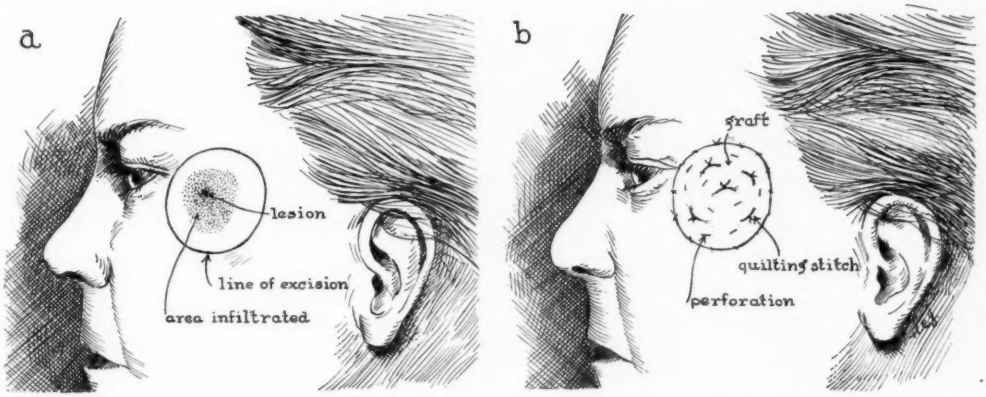

Fig. 1. Case 1. a, Diagram showing extent of lesion under normal appearing skin. b, Method of immediate application of free full thickness skin graft, following surgical excision.

time there was no evidence of recurrence, and the edges of the defect following slough from x-ray therapy gradually cleaned up and healed. During this period of time he received heavy antiluetic treatment.

On June 23, 1936, a forehead flap was partially elevated and delayed. On August 11 a second elevation of the flap was carried out. On August 25 elevation of the flap was completed. All 3 of these steps were done under local anesthesia. On September 17, 1936, the flap was judged to be in satisfactory condition for transfer, and on that date the margins of the defect were widely excised and the forehead flap was turned down into place. It had grown into place securely by October 6, 1936, and on this day the pedicle was returned to the forehead and the remaining defect was grafted with a split graft from the thigh. Both these steps were carried out under avertin plus ether anesthesia. Trimming operations on the reconstructed right half of the nose were done on January 7, 1937, and April 8, 1937, under local anesthesia.

This patient has been carefully followed and to date, approximately 4 years later, there has been no recurrence.

Case 3. E. H., S. M. H. No. 91,783. A 61-year old housewife entered the clinic June 22, 1938, because of the return of a "lump" in the right eyebrow. Eleven years before, she had what she thought was a small mole just above the right eyebrow which she picked with a pin. Two to 3 months later she noticed that the mole was becoming larger. She went to a physician who told her that she had a tumor about the size of a dime beneath the skin and removed it by fulguration. She then had no trouble for about 9 years. About 2 years ago she noticed that the scar above the eyebrow was enlarging and becoming lumpy. This enlargement has slowly but steadily increased. She has no other symptoms than the increase in size of the area above the eyebrow.

General examination showed that she had moderate arteriosclerosis and cardiac hypertrophy, but no other abnormalities than the growth above the right eyebrow.

There was a scar about 1 centimeter in diameter just above the middle of the right eyebrow. The center of this was slightly crusted, but not ulcerated. Extending outward from this scar was a firm subcutaneous thickening. This hardness extended under most of the eyebrow. The skin over it was perfectly normal. A biopsy was done and was diagnosed basal cell carcinoma.

Fig. 1c. Case 1. Basal cell carcinoma recurrent three times during 7 years. Left photograph shows condition present after third recurrence. Right photograph shows appearance of an off color free full thickness skin graft 1 year after surgical excision and repair. No recurrence to date (3 years).

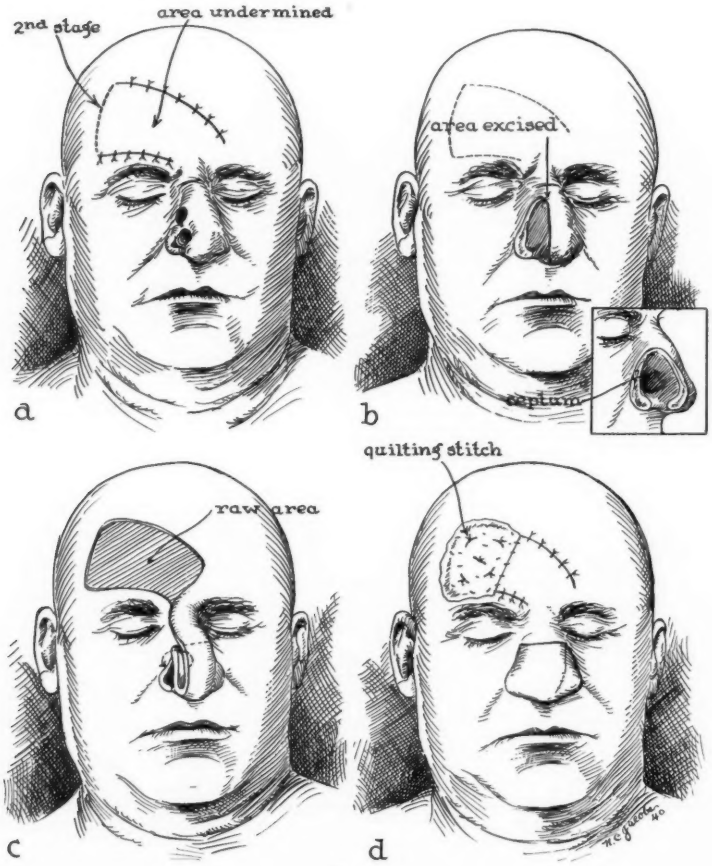

Fig. 2.

Fig. 2e.

Fig. 2. Case 2. a, Forehead flap delayed on two occasions. b, At third operation the lesion is excised with a wide margin of good tissue, and, c, the flap previously prepared is immediately used to repair the loss. d, After the flap has securely grown in place, the pedicle is divided and that portion not used is returned to its original site. The remaining raw area on the forehead is covered with a free split thickness skin graft from the thigh.

Fig. 2e. Case 2. Left photograph, nasal loss due to basal cell carcinoma following radiation therapy. Right photograph, final result 1 year after wide excision and repair. Patient now over 4 years without recurrence.

On July 14, 1938, the lesion was excised. This method of eradication was decided on in consultation with our radiologist; he was of the opinion that the proximity of the eye and the extent of the

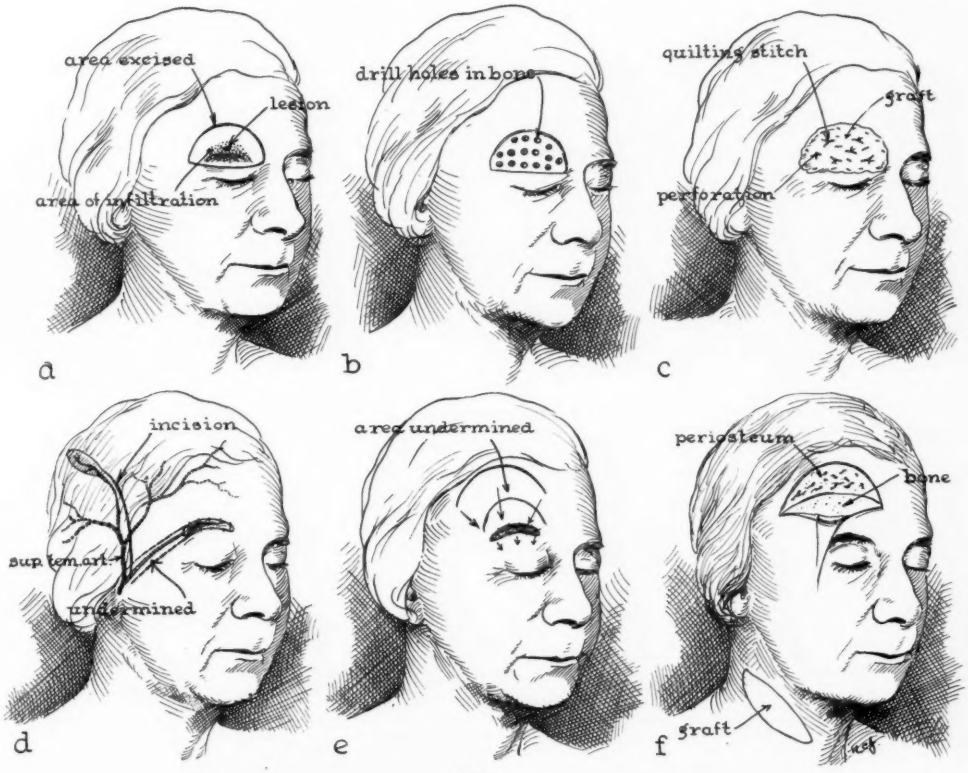

Fig. 3.

Fig. 3g.

Fig. 3. Case 3. a, Diagram of extent of lesion, necessitating complete excision of eyebrow and surrounding skin down to skull, and, b, numerous drill holes in skull to allow granulations to grow up from cancellous bone. c, Five weeks later granulating area epithelized with split thickness free skin graft from thigh. d, Three months later eyebrow reconstructed by transplantation of temporal artery and vein carrying an attached piece of hair bearing tissue from the scalp. e, About 4 months later reconstructed eyebrow and adjacent skin slid downward, by undermining through incision just below hairline, to relieve tension on upper lid and, f, free full thickness graft taken from neck, used to close resulting gap of forehead skin below hairline.

Fig. 3g. Case 3. Left photograph, granulating area after excision and bone drilling. Right, 1 year after repair; eyebrow satisfactory; 2½ years to date without recurrence.

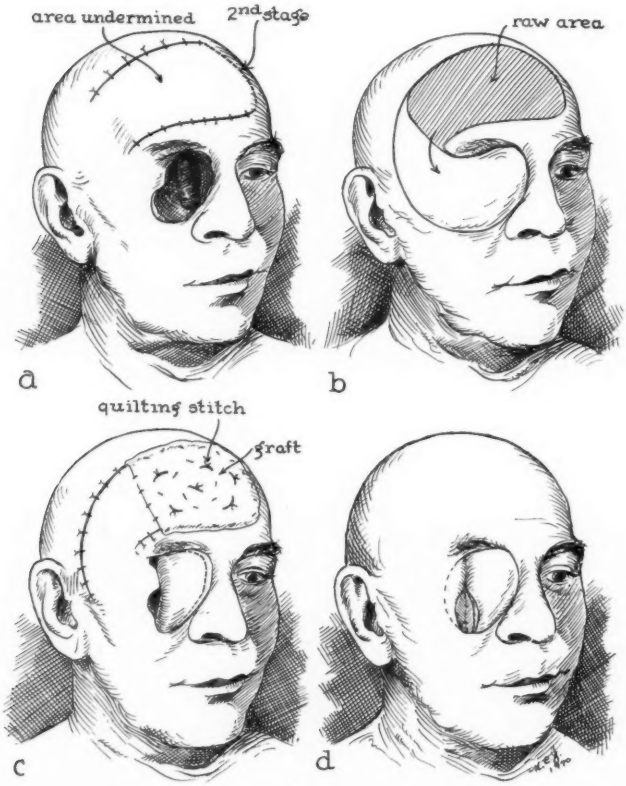

Fig. 4.

Fig. 4e.

Fig. 4. Case 4. a, Exenteration of orbit and ethmoidal region because of basal cell carcinoma invading bony floor and medial wall of orbit. Two weeks later forehead flap

(*Legend continued on opposite page.*)

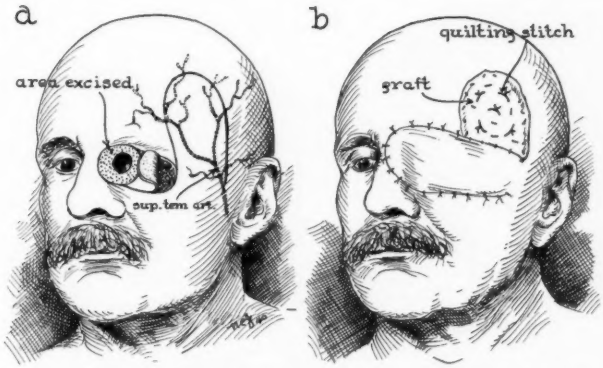

Fig. 5. Case 5. a, Diagram showing extent of soft tissue and bone excised and flap of skin and subcutaneous tissue raised laterally and turned over to provide lining. b, Forehead flap containing temporal vessels rotated for external skin and the site from which this came grafted with a split thickness graft. When major vessel bearing flaps are obtainable, eradication and repair can be safely done in one step.

growth contra-indicated radiation therapy. In order to allow a satisfactory margin of good tissue about the growth, the entire eyebrow and the superior portion of the upper eyelid were removed down to the skull. The bone was drilled in numerous places to permit granulations to form. Thirty-five days later the bed of granulations was satisfactory and a split graft from the thigh was applied. This took completely. Three months later, after the graft had softened, the eyebrow was reconstructed by an arterial scalp pedicle graft. A few hairs at the distal (medial) end of this were lost but the result on the whole was quite satisfactory. However, after several months had passed, it was apparent that there was a tightness of the upper lid due to insufficient tissue and that the eyebrow was somewhat too high in relationship to the normal of the other side. About 4½ months after restoration of the eyebrow, the final operative step was done. An incision was made just below the hairline on the right side and a large flap of skin and frontalis muscle dissected free down to the upper eyelid. In the upper portion the pericranium was left intact. In the lower portion the graft adherent to bone was freed and the whole mass including eyebrow was slid downward. A free full thickness graft from the neck was used to fill the gap just below the hairline. This resulted in the necessary laxity of the upper eyelid and an improved lower position of the eyebrow. The patient has been followed, and to date, 2 years after excision of the growth, there has been no recurrence of the growth.

Fig. 5c. Case 5. Left photograph shows the sixth recurrence of a basal cell carcinoma on the nasal margin of a defect produced during previous treatment. Right, result following surgical excision and closure carried out in one operation. No recurrences to date, about 2 years afterwards.

Case 4. F. N., S. M. H. No. 40,290. A white, male farmer first entered the clinic in October, 1930, because of a gastric ulcer for which gastric resection was done. At that time a few small pearly nodules were present at the internal canthus of the right eye. These were treated by x-ray, and the patient was given an appointment to return in 2 weeks for radium therapy. For some reason this treatment was not given although he was seen quite frequently in the clinic for follow-up of his gastric status. In August, 1933, he had an obvious recurrence of the rodent ulcer, and he was given 100 milligram hours of radium radiation. The lesion recurred promptly

delayed in two stages. b, Four weeks later flap transferred and sutured to freshened edges of defect. Forehead left to granulate. c, Five weeks later, pedicle severed and rolled under to form defect lining; remainder of flap returned to forehead; rest of granulating forehead covered with one large split thickness skin graft. d, Six weeks later lateral opening into defect closed in two layers, completing lining and covering.

Fig. 4e. Case 4. Left photograph shows many times recurrent basal cell carcinoma which by x-ray had extended into bones of orbit. Right photograph, result 2 years after repair. No recurrence in 3 years.

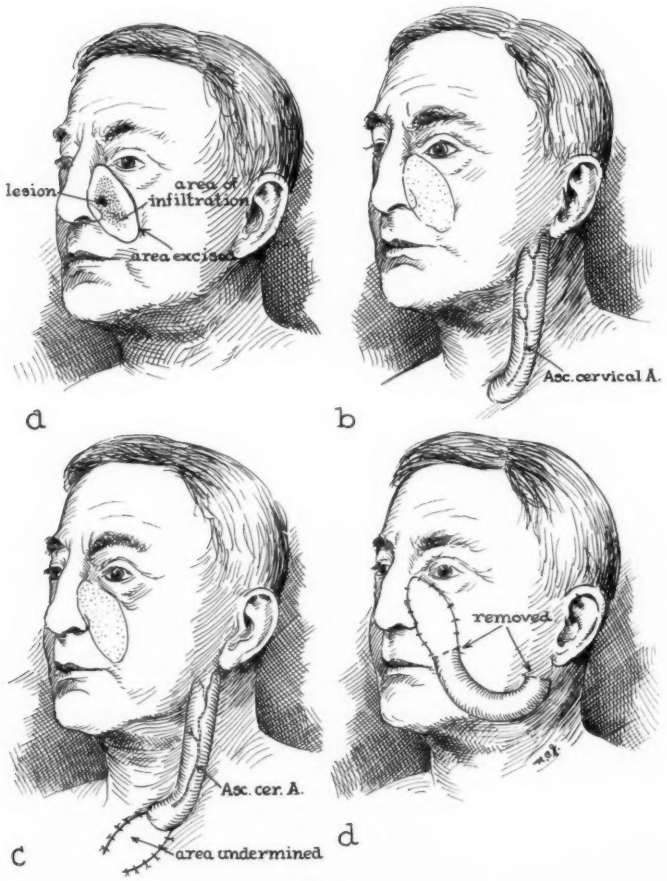

Fig. 6.

Fig. 6e.

(*Legend on opposite page.*)

and in January, 1934, it was destroyed by electrocoagulation.

Within 6 months the growth was again present. He was treated again by applications of radium. He did not appear in the clinic for about 2½ years. When seen at this time, August 17. 1937, there was recurrence of the growth with fixation to the inferior medial orbital rim. X-ray films of the region showed involvement of the infraorbital rim by tumor. It was decided that the only chance of arrest of the growth was by radical surgery, and I saw him for the first time on this occasion. An exenteration of the orbit along with the growth was advised. This was carried out in September, 1937. Two weeks afterward a large flap, with its pedicle including the frontal branches of the temporal artery, was delayed on the forehead. Three weeks later the distal end of the flap was cut across under local anesthesia. A week later the flap was transferred to the defect. Five weeks after the pedicle of the flap was divided and doubled under to line the inner surface of the flap with epithelium. The remainder of the pedicle was returned to the temporal region and the granulating area on the forehead grafted with a single split thickness skin graft.

These wounds all healed nicely and 6 weeks later the opening left laterally was closed. The patient was seen in June, 1939, approximately 2 years following removal of the tumor. At that time he complained of a bad odor in the nose and difficulty in getting rid of this. Intranasal examination showed that this was due to crusting and detritus in the large cavity under the repair. He was advised as to how to cleanse the cavity. There was no recurrence at that time.

CASE 5. F. T., S. M. H. No. 34,006. A white, male laborer, aged 60 years, was first seen in the clinic in April, 1930, because of a growth in the region of the inner canthus of the left eye. This had been present for 5 years. During this time no treatment other than a protective dressing had been used. He complained that he had rather severe shooting pains in the growth and that it itched. At times it crusted over and seemed to him to be healing.

The growth was ulcerated, moist, red, and covered the entire left internal canthal area and most of the left side of the nose, the edges were rolled, and it was about the size of a silver dollar. The eyelids could be closed but could be opened only about one-fourth of normal. There were no other abnormalities of consequence on general examination.

A biopsy was diagnosed as carcinoma of intermediate type. The sections were not typically squamous cell in type but seemed to be more malignant than the usual rodent ulcer.

Treatment was by unfiltered contact radium during the last 6 months of 1930. Approximately 300 milligram hours total of radium irradiation was given at about monthly intervals. The majority of the tumor healed but one small, apparently radioresistant, area remained. This was removed by electrodesiccation in January, 1931. By the first of April, 1931, it was obvious that the growth had recurred. At this time a local excision of the recurrence was done. By September of this year, there was a probable recurrence which was treated by radium for 450 milligram hours. There was then no recurrence for a year, and the patient did not appear again in the clinic until August, 1933. At this time he had a small growth about 3 millimeters in diameter on the conjunctival aspect of the lower eyelid. He was treated with 40 milligram hours of radium and was to report in 6 weeks. He did not return, however, until about 1 year later, and he again had a large obvious recurrence. At this time the radiologist stated that he did not believe the growth could be controlled by radiation alone, but because surgery would have to be "extensive and mutilating," a maximum dose of radium was applied. The dose given was 8,225 milligram hours. In spite of this there was a persistence of the growth at the internal canthus and in October, 1935, about 1 year after the massive dose of radium, a subtotal exenteration of the orbit and evisceration of the ethmoid cells were done. Following this he had no recurrence for a period of about 3 years. In December, 1938, he returned with an ulcer on the bridge of the nose which extended from the margin of the previous operative defect to the midline. In one area the ulcer edge was irregularly elevated, and a biopsy from this site showed basal cell carcinoma.

I first saw the patient at this time, and in going over the situation with the radiotherapist, we summarized the matter as follows: a proved basal cell carcinoma, recurrent numerous times over a period of 8 years, had been treated with a total of about 9000 milligram hours of radium and in spite of this treatment plus local surgery, carcinoma was still present. In view of these facts we both felt that further radiation was certainly not indicated. We therefore advised that a wide excision of the involved area and immediate repair be carried out.

In December, 1938, I excised the area and repaired it. This was accomplished by making an incision through good tissue about ½ inch beyond the ulcerated area down to bone. A corresponding rim of bone was removed attached to the soft tissues and the entire excised area lifted out in one piece. A flap of skin and subcutaneous tissue was then cut lateral to the defect with its pedicle near the defect margin. This flap was turned medially with its epithelial surface inward and sutured to small drill holes made in the nasal bone; thus lining of the

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Fig. 6. Case 6. a, Extent of infiltration of persistent basal cell carcinoma. b, Tubed flap formed on neck. c, Flap attached to tube delayed. d, Area outlined in, a, excised and at once repaired with delayed flap, nourished by previously constructed tube graft. The nourishing tube after 2 months was excised and discarded.

Fig. 6e. Case 6. Left photograph, indolent ulcer with wide zone of infiltration persistent in spite of radiation therapy. Right photograph, result after full thickness excision of soft tissues and repair. No recurrence in 3 years.

cavity was provided. The frontal branch of the temporal artery was now traced by palpation and a flap of skin and subcutaneous tissue was cut from the left temporal region just anterior to the hairline which included this vessel. This flap was turned downward over the raw surface of the lining flap and sutured to the edges of the defect. A split graft from the thigh was used to cover the raw area on the left temple. These flaps and the graft all took well and the patient's total hospital stay was only 27 days. Since that time to the present, roughly 2 years, he has been examined frequently and, as yet, there is no recurrence.

CASE 6. D. S., S. M. H. No. 67,597. This 68-year old man first entered the clinic in September, 1933. At that time he had facial erysipelas which had started in an open wound in the left nasolabial fold. This wound, the patient stated, was due to a laceration received in an automobile accident 10 months previously which had never healed completely. On closer questioning it was found that he had had an indurated area with a dark center in the nasolabial fold for 10 years or more, and that the so-called accidental laceration had more probably been a rupture of the area. It was also discovered that he had moderately severe diabetes. At that time it was thought that there might be a foreign body in the wound preventing its healing, but due to the erysipelas, exploration of the wound was postponed for 6 months.

In 6 months' time, as agreed, he returned and at that time the lesion on the left cheek extended from the left internal canthus down the nasolabial fold to almost the corner of the mouth. It was quite indurated and about 2 centimeters wide. At about its midpoint there was a small ulcer. A biopsy examination of the ulcer edge was taken and found to be basal cell carcinoma.

Radiation therapy was started at once to the amount of 1,625 milligram hours. Filtered radium was given. He was followed closely over a 3 year period. The induration never entirely subsided, and during the last half of the third year it was evident that the indurated area was spreading.

Because of the depth to which this induration seemed to extend, it was decided that wide surgical excision offered the best chance of cure. I, therefore, planned to develop a tubed flap prior to excision and thus be able to remove the growth widely and to repair the loss at the same time. In October, 1937, a vertical tube was constructed on the left side of the neck. About 1 month later a flap corresponding in shape to the area to be excised was delayed at the lower end of the tube. This showed no vascular difficulties whatever, and 3 days later the indurated area along with a ½ inch margin of normal tissue was excised in one piece. This block of tissue was peeled off the bone, all muscular tissue being removed along with the growth. In the alar region the full thickness of the nose had to be removed to be safe. This left a small opening the edges of which were sutured in a somewhat make-shift manner; the chest end of the tube was then used completely to repair the defect. Sections of the removed block of tissue showed basal cell carcinoma invading the facial muscles.

After operation some infection developed under the flap. This cleared slowly under saline compresses and close attention to his diabetic regimen. Due to scar contracture following the infection, the flap tended to bunch up rather than remain in flat position. About 2 months later the tube attachment was severed and by undermining the edges of the transplant this bulging was corrected. The remainder of the tube not used on the face, was excised and discarded.

He has been followed now for approximately 3 years. There is a moderate asymptomatic ectropion of the left lower eyelid. The transplant has remained soft and as yet there is no evidence of recurrence.

A FIVE YEAR SURVEY OF THE BLOOD SEDIMENTATION TEST IN ACUTE APPENDICITIS

ALBERT LESSER, M.D., and LOUIS RENE KAUFMAN, M.D., F.A.C.S., New York, New York

IN 1935 a paper on the blood sedimentation test and its value in the differential diagnosis of acute appendicitis was published by one of us. In this study it was observed that the blood sedimentation rate in acute appendicitis without rupture, whether catarrhal, suppurative, or gangrenous, was uniformly *normal*, whereas all other conditions producing the clinical picture of the acute surgical abdomen showed a definitely abnormal sedimentation reaction. In 1937 Bannick, Gregg, and Guernsey published a confirmation of our observation based upon a 2 year survey of acute appendicitis at the Mayo Clinic.

We are now submitting a supplementary report on the blood sedimentation test in a series of cases in which patients were operated upon for acute appendiceal pathology, in the 5 year period from 1935 to 1939. This present series of cases, like the original group, was studied at the Metropolitan Hospital, and the same gradations of readings, as previously established by the Westergren technique, were used, as follows: 6 millimeters to 15 millimeters in the hour, normal reaction; 25 millimeters to 40 millimeters in the hour, moderate reaction; 60 millimeters to 80 millimeters in the hour, high reaction; 80 millimeters to 140 millimeters in the hour, severe reaction. For purposes of simplification the technique of the Westergren method was slightly modified so that 4 cubic centimeters of blood was added to a test-tube containing 1 cubic centimeter of 3.8 per cent solution of sodium citrate. There was one circumstance in the performance of the tests, however, that differed from conditions existing in the original study: since sedimentation tests had become routine procedure for acute surgical admissions, they were performed by a large number of individual internes each of whom spent a relatively short time on the surgical service during their rotating internship. The results represent, therefore, a measure of the average accuracy of technique of a fairly large number of individuals rather than the constant degree of accuracy of one or two individuals (in the original study all tests were performed by the authors).

This report presents 132 cases of patients operated upon with a preoperative diagnosis of acute appendicitis or primary appendicular pathology. In 15 of these cases the preoperative diagnosis was erroneous, operation revealing pathological condition other than appendicitis. As demonstrated in the original report, the conditions most commonly responsible for confusion with acute appendicitis were acute salpingo-oophoritis, acute inflammatory chest conditions, tuberculosis—pleural or abdominal—pyelitis, mesenteric adenitis, and acute rheumatic fever. In these 15 extra-appendiceal conditions the sedimentation readings were consistently elevated or high, as differentiated from the normal readings found in acute appendicitis. In 8 cases there were complicating appendiceal abscesses, and in 10 cases there were found generalizing peritonitis of varying degree and severity. Again it was noted, as in the original study, that all cases complicated by abdominal abscess or peritonitis showed a consistently elevated blood sedimentation rate varying from high to severe reaction.

In 99 cases the preoperative diagnosis of acute appendicitis was verified by the operative findings, revealing an acute catarrhal, suppurative, or gangrenous appendix. In 90 of these cases the blood sedimentation rates were 15 millimeters, or less, in the hour; that is, within the absolute normal as previously established. In 9 cases the blood sedimentation rates were slightly above 15, the readings varying from 21 to 26 millimeters in the hour. We believe that this very slight deviation

From the Department of Surgery, New York Medical College, Flower and Fifth Avenue and Metropolitan Hospitals.

from the absolute normal in a small percentage of cases may be explained by minor inaccuracies or deviations from precise detail of technique on the part of the large number of internes called upon to perform these blood sedimentation tests as a routine of the admission work-up; such minor inaccuracies of detail may consist of inexact proportions of blood and sodium citrate, lack of proper cleanliness of the sedimentation tubes, and prolonged standing of the citrated blood before performing the test. We offer this explanation only to stress the fact that these tests were performed not by a small number of laboratory technicians, but rather by many first year internes in whom slight inconstancies of laboratory technique may be expected.

SUMMARY

1. The routine use of the blood sedimentation test has contributed to the more accurate differential diagnosis of the acute surgical abdomen, and particularly, of acute appendicitis.

2. A consistently *normal* blood sedimentation rate in acute appendicitis has been corroborated in more than 90 per cent of cases in a survey covering a 5 year period.

3. A small percentage of cases show a slight elevation from absolute normal; this circumstance may be due to minor deviations from details of technique, as a result of routine ward usage, and in any event does not affect or alter the significance of a *low* or *minimal* blood sedimentation rate in *all* cases of acute appendicitis.

4. Acute adnexal disease, the condition most commonly to be differentiated from acute appendicitis in acute abdominal cases routinely admitted to the surgical service of a large municipal hospital, has come to needless and frequently harmful operation much less frequently as a result of increasing awareness of the blood sedimentation test.

5. As previously observed, there is no relationship between leucocytosis and the blood sedimentation reaction.

6. This survey of cases over a 5 year period further substantiates the importance of the blood sedimentation test in the differential diagnosis of acute appendicitis, and warrants its continued use and clinical application.

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OCCURRENCE OF POSTOPERATIVE ACIDOSIS AND PAGETOID BONE CHANGES IN HYPERPARATHYROIDISM

J. H. COUCH, M.A., M.B. (Tor.), F.R.C.S. (Ed. & C.), and
H. F. ROBERTSON, M.B. (Tor.), B.Sc. (Med.), F.R.C.S. (C.), Toronto, Canada

TWO cases of parathyroid tumor associated with hyperparathyroidism are presented with a discussion of two important and as yet unstressed aspects of this syndrome. One case brings out clearly the dangers of acidosis in such cases, and it presents as well many of the factors which make these cases difficult to diagnose and to treat. The other case illustrates a rare and easily missed type in which the skeletal lesions in many ways resemble those of Paget's disease.

The occurrence of acidosis as a sequela of parathyroidectomy in hyperparathyroidism is probably not rare and when it does appear is a very dangerous complication. Though there are many accounts of anuria, terminal nephritis, and uremia, associated with the various kidney lesions in the disease, little has been said about retention of acid radicals in, or the loss of the alkaline radicals from, the acid-base neutralizing mechanism of the body (1, 2, 7, 8, 9). This mechanism as well as its relation to acidosis in patients after parathyroidectomy is discussed, in an attempt to explain the cause of the acidosis and to outline certain preoperative and postoperative measures for its prevention.

Pagetoid bone changes associated with a hyperfunctioning parathyroid adenoma have been described infrequently in the literature (3, 6). Though in hyperparathyroidism decalcification is usually steadily progressive and widespread, at times it seems that it progresses more rapidly in one bone than another, and again there may be periods of quiescence or even recalcification. Such episodes simulate Paget's disease in an x-ray study of the skeleton. In the cases of Gutman and Parsons, Paget's disease actually did play a part, but in the case here reported there had never been any indication of Paget's disease other than the simulation in the roentgenograms.

CASE REPORTS

The first case illustrates the difficulties surrounding the diagnosis of parathyroid adenoma associated with hyperparathyroidism, the difficulties and the methods of finding such a tumor at operation, the dangers attendant on, and the treatment of, the postoperative chemical disturbances, and the happy culmination to be expected following successful treatment.

The signs and symptoms of hyperparathyroidism are conveniently divided into three groups: (1) those which relate to the presence of hypercalcemia; briefly, depression of all neuromuscular functions; (2) those due to loss of calcium from the skeleton: namely, generalized rarefaction of bones; (3) those due to a damaged kidney, called upon to excrete a heavy load of calcium daily; for example, impaired kidney function, renal metastatic calcification, nephrolithiasis, or acidosis.

The patient in Case 1 followed these in turn.

CASE 1. Mrs. B., aged 52 years, was admitted to Toronto General Hospital, May, 1939, complaining of increasing lassitude, muscular weakness, loss of appetite, and a loss of 50 pounds in weight. Physical examination showed cachexia, and achlorhydria with a hemoglobin of only 30 per cent. Although this group of symptoms and signs was probably due to a high serum calcium level it was not sufficient to lead to the true diagnosis.

The patient improved on iron and was sent home for 6 weeks. She then showed the second group of signs; namely, that due to loss of calcium from the skeleton. Her bones had lost so much calcium that she suffered a fracture of the femur. On readmission to hospital, it was noted that her skull could be dented like rubber and her ribs fell in instead of lifting on inspiration.

Blood chemical studies showed serum calcium increased to twice normal, serum phosphorus decreased to half normal, phosphatase increased to four times normal (Table I and Figs. 1 and 2).

A detailed study of calcium balance, carried out by the Department of Medicine at the Toronto General Hospital, proved that, on ordinary diet, the patient was excreting five times the amount of cal-

TABLE I.—PARTIAL SERUM CALCIUM PHOSPHORUS, PHOSPHATASE, AND CALCIUM METABOLISM—CASE 1, Mrs. B.

Period	Dates	Volume urine	Weight feces	Urine calcium	fecal calcium	Calcium output	Calcium intake	Calcium balance	Serum calcium	Serum phosphorus	Phosphatase
					Preoperative						Kay units
1	6–18–1939 6–21	1433	11.0	363	203	566	47	−519	14.6	1.8	52
	CO_2 C. P. 40% to 47% Vol.										
3	6–24 6–27	1390	7.0	445	117	562	87	−475	14.3	1.9	
5	6–30 7– 3	1483	8.1	319	107	426	88	−348	15.1	1.7	54
7	7– 6 7 9	1393	10.1	267	404	671	1231	+560	14.9	1.8	57
	A. T. 10 started July 12										
					Postoperative						
	7–13								12.6	2.1	50
	7–14								7.2	4.1	56
	7–15				CO_2 C. P. 19% vol. CO_2 C. P. up to 57% vol. Chvostek positive Ca. lactate started				6.5	4.7	
	7–16								6.3	4.5	27
	7–17								7.0	4.3	28
	7–18								7.6	4.0	13
12	7–22 7–25	966	13.0	35	622	657	2937	+2280	8.5	4.0	39
17	8–19 8–25	1085	10.6	25	367	392	2307	+1915	8.0	3.9	19
	A. T. 10 stopped Sept. 21										
30	12–26 1– 6–1940	840	26.3	46	1294	1340	2703	+1363	10.0	3.3	4
35	2–16 2–26	816	38.2	39	1898	1937	2692	+755	9.7	3.4	10
	Viosterol started										
38	3–18 3–28	775	25.5	52	1015	1067	2700	+1633	9.5	3.6	4
	On 1 capsule calciferol for 2 weeks										
44	5–17 5–28	757	19.6	55	997	1052	2667	+1615	10.6	3.3	9
	On 2 capsules calciferol for 3 months										

cium she was imbibing each day, the excess being removed from the skeleton (Table I). Roentgenograms of the skeleton revealed widespread and advanced rarefaction and multitudes of tiny bone cysts, besides one large cyst at the site of fracture (Fig. 3). A biopsy specimen of bone was taken from the fracture site and a diagnosis of osteitis fibrosa cystica made. Kidney function tests, before operation, showed a specific gravity range of 1009–1012, and again 1010–1013, with day and night urine excretion amounts almost equal the first time, and the day urine volume twice the night urine volume the second time. Nonprotein nitrogen in the blood, before operation, ranged from 43 to 47 milligrams per cent. Carbon dioxide combining power of the blood ranged from 40 to 47 volumes per cent before operation. Blood sodium before operation was 268 milligrams per cent.

The diagnosis of hyperparathyroidism was therefore established with surety by the finding of a consistently elevated serum calcium, a consistently low serum phosphorus, a consistently high phosphatase reading, a persistently negative calcium balance, diffuse skeletal decalcification, and a biopsy of bone tissue confirming the presence of osteitis fibrosa cystica (3, 6). It remained then the surgeon's task to complete the clinical picture by finding the tumor. It was borne in mind that more than one patient has been operated on repeatedly because removal of unconfirmed tissue, or normal parathyroid tissue, failed to relieve the symptoms, and that each operation is attended with a definite risk. Therefore, the

plan was followed of searching the usual sites first, the easily explored areas around the thyroid gland second, and then the thyroid gland itself before contemplating the potentially dangerous maneuver of retrosternal examination.

The tumor was not visible or palpable on exposure of the thyroid area, and biopsy of numerous superficial and suspicious thyroid nodules did not reveal a parathyroid tumor. The region around the thyroid from hyoid to sternum was thoroughly examined, the prevertebral fascia being opened also. No tumor was evident. Therefore, the right thyroid lobe was resected and examined in the gross and by quick section by the pathologist. As no parathyroid tumor was found, the left lobe was resected, and finally the tumor was discovered completely imbedded in thyroid tissue. Operation was not prolonged in spite of these difficulties and the patient was returned to bed in good condition (Fig. 4). Microscopic examination showed the tumor to be composed of cords and irregular masses of oxyphil cells (Fig. 5).

Ten hours after operation the patient manifested the third group of symptoms mentioned; that associated with acidosis. Breathing suddenly commenced to become more rapid and shallow, the pulse rate mounted quickly, the blood pressure was increased to 160/70 millimeters of mercury. The patient soon became unconscious. Carbon dioxide combining power was found then to be only 19 volumes per cent. The blood chloride estimation was 800 milligrams per cent. There was no evidence of tetany. Blood serum 5 hours after operation had shown a calcium of 12.6 milligrams per cent, phosphorus of 2.1 milligrams per cent, and a phosphatase of 50 units (Kay). Surgical shock was not present.

To combat this condition 500 cubic centimeters of 5 per cent sodium bicarbonate in distilled water was given slowly intravenously and in 1 hour the patient was again conscious, fairly bright, with a pulse of 100 and normal respirations. A carbon-dioxide combining power determination done a few hours after recovery read at 56 volumes per cent, while later in the first day after operation it was 60 volumes per cent. The blood chloride estimation a few hours after recovery from acidosis, was 575 milligrams per cent. The nonprotein-nitrogen of the blood was 54 and 47 milligrams per cent the day after operation.

No recurrence of acidosis threatened. The carbon dioxide combining power remained between 52 and 57 per cent, by volume, for the first week after operation and during the next few months ranged from 45 to 67 volumes per cent. Nonprotein-nitrogen estimations varied between 32 and 57 milligrams per cent. Four days after operation the blood sodium reading was 299 milligrams per cent, while 10 days afterward it was read at 350 milligrams per cent.

There was a variable and barely noticeable Chvostek's sign present on the second postoperative day when the serum estimations were: calcium 6.5, phosphorus 4.7 milligrams per cent. This sign was occasionally present until the tenth postoperative day during which time calcium lactate and ditachysterol were given and continued thereafter. As shown in Table I the serum calcium ranged during this time from 6.3 to 8.5, while phosphorus ranged from 4.7 to 4.0 milligrams per cent.

The patient's progress was very satisfactory from the first day after operation. Besides a return to normal serum calcium and phosphorus content, the phosphatase reaction more gradually returned to normal (Table I, Figs. 1 and 2). The patient's melancholia disappeared entirely. Her cachexia rapidly vanished. Her fractured femur progressed to union gradually. Roentgenograms a year after operation showed progressing recalcification of all bones, although the femora still showed some areas of cyst formation (Fig. 3).

The second case illustrates how, in hyperparathyroidism, the bony changes may simulate those of Paget's disease.

CASE 2. Mrs. McK., aged 64 years, was admitted to St. Joseph's Hospital, Toronto, April 1939. She had fallen on her right hip earlier in April, 1939. Though bruised slightly, she carried on for several weeks when her physician suggested that x-ray study was advisable because of the continuing soreness in hip and of a long continued aching pain in both lower limbs. Examination prior to the x-ray study revealed only slight tenderness over the right greater trochanter and questionable limitation of movement of the right hip joint. An x-ray film of the affected hip was reported as showing the changes of osteitis fibrosa cystica (Fig. 6). Besides the bone cysts there could also be noted some laying down of new bone beneath the cortex of the femur, particularly in several parts of the pelvis. With this film in mind the patient was then re-examined. A story of aching bones, with loss of about 3 inches in height without much change in hat size in several years, gradually increasing muscular weakness, general wasting, the loss of 30 pounds weight in a few years with loss of appetite and bouts of nausea and constipation, along with a tumor in the right lower neck anteriorly, made one suspicious of the presence of hyperparathyroidism, and the patient was admitted for investigation.

Further study of the patient in the hospital elicited the following facts: For many years she had had infrequent exacerbations of rheumatic heart disease with several periods of cardiac insufficiency. Mitral stenosis was present. There was no day or night frequency of urination or other evidence of kidney failure in the patient's history. Routine urine and kidney function tests revealed a variation in the urine's specific gravity, between 1003 and 1012, with a fair, though slightly altered, balance between day and night volumes. Nonprotein-nitrogen determinations varied within normal limits. Carbon dioxide combining power estimations indicated a normal alkaline reserve.

Additional x-ray films taken in the hospital showed decalcification of all the long bones, and decalcifica-

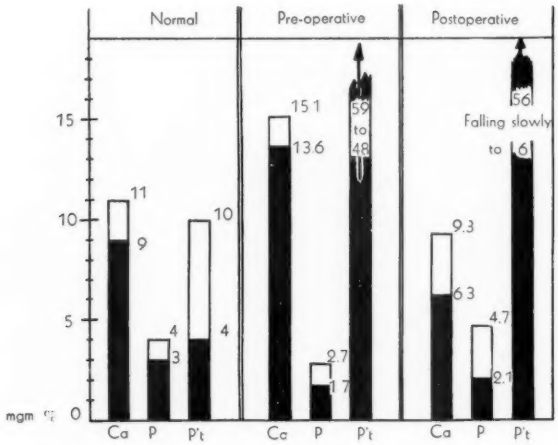

Fig. 1. Diagrammatic representation of serum calcium, phosphorus and phosphatase figures in normal and in Case 1 before and after parathyroidectomy.

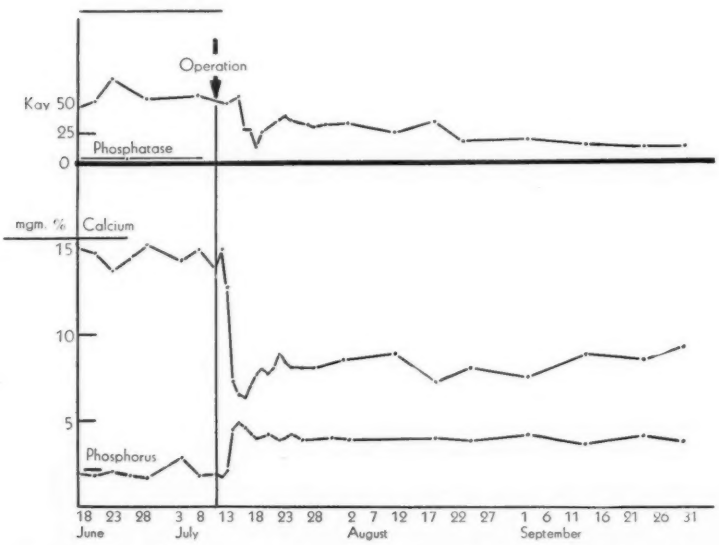

Fig. 2. Graphic representation, of serum calcium, phosphorus and phosphatase, before and after operation in Case 1.

tion of the spine, but no vertebra was actually collapsed. No bone cysts were present except in the pelvis and the femora.

The skull roentgenogram was typical of many others taken in cases of hyperparathyroidism. There were wide mottled areas of decalcification without regions of recent bone deposition and without the "cotton wool" appearance characteristic of Paget's disease. Thickening of the cranial vault with separation of the outer and inner tables was also seen as is common in hyperparathyroidism.

Chemical investigations were carried out by Mr. Wakefield at the Toronto General Hospital and by Dr. Farquharson and Mr. Simmons of the Depart-

Fig. 3. Roentgenograms of left femur of Mrs. B., Case 1, 2 months before and 8 months after parathyroidectomy.

Fig. 4. Left thyroid lobe with parathyroid tumor imbedded in pole in Case 1.

ment of Medicine, University of Toronto. A constantly elevated serum calcium content and phosphatase reaction were present with a lowered serum phosphorus content. On a low calcium intake diet the patient constantly maintained a negative calcium balance (Table II, Fig. 7).

These data in conjunction with the history and physical findings, including the lump in the right neck, pointed strongly to a diagnosis of parathyroid tumor causing hyperparathyroidism.

For a week prior to operation a high calcium intake diet, along with viosterol, was given, in an attempt relatively to reduce the calcium loss from the body. The efficacy of such treatment is perhaps not too well proved and some think it may lead occasionally to calcification of tissues, particularly renal tissues. Also, for some time prior to operation, the patient was placed on a salt free diet in order to guard against possible acidotic, nephritic, and cardiac complications.

Operation was done under local anesthesia in order to minimize the operative risk. A large tumor 3 by 2 by 1.5 was found easily, lying a little posterior to the right lower thyroid pole. The tumor was outside the thyroid capsule, was grayish white in color, and was lobulated (Fig. 8). It was supplied by a small branch of the inferior thyroid artery. Quick section confirmed the gross pathological diagnosis. No other tumors were noted.

Microscopic examination of the specimen revealed fairly typical parathyroid tumor tissue of the primary type. Acinar arrangement was common but many long strands of cells were also seen. Scattered oxyphil cells and large water-clear cells were present (Fig. 9).

The postoperative course was quite uneventful. Patient was up and about the second day. There was no evidence of tetany, acidosis, or of kidney failure. The blood chemical changes and the calcium balance changes were quite normal for such a patient, the serum calcium and phosphorus becoming rapidly normal and the phosphatase reaction gradually returning to a normal level. Measurement of urine calcium excretion indicated a positive calcium balance (Table II, Fig. 7); postoperative roentgenograms, rapid laying down of calcium in bones with obliteration of areas of cyst formation (Fig. 10).

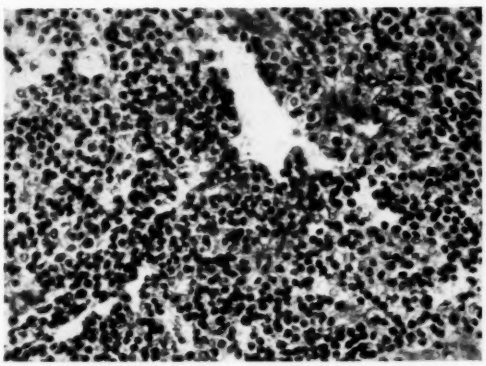

Fig. 5. Photomicrograph of section from parathyroid adenoma in Case 1.

TABLE II.—SERUM CALCIUM, PHOSPHORUS, PHOSPHATASE AND CALCIUM METABOLISM—CASE 2, Mrs. McK.

Period	Dates	Volume urine	Weight feces	Urine calcium	Fecal calcium	Calcium output	Calcium intake	Calcium balance	Serum calcium	Serum phosphorus	Phosphatase
		Preoperative									
I	5– 5–1939								13.7	1.4	Kay units 75.5
	5– 9	423	16.3	197	122	299	100	−199			
	5–10								11.3	2.1	60.2
II	5–11	CO_2 C. P.—56% Vol.									
	5–12 5–13 5–14	663	9.7	208	58	266	100	−166			
	5–15								12.4	2.0	77.0
III	5–16 5–17	610	8.9	218	74	292	100	−192			
	5–19								11.6	2.4	86.0
	5–25								11.6	2.5	79.0
		Postoperative									
	5–29								10.6	2.8	61.0
	5–30								10.0	3.2	
	5–31								8.9	3.5	
	6– 2								7.7	4.0	
	6– 7								8.4	3.9	
	6–14								9.2	3.4	
	6–21								10.6	3.4	
I	6–27 6–29 6–30	1967		63				Positive			
II	7– 1 7– 2 7– 3	1233		40				Positive			
	10–20								10.4	3.4	10.0
	8–10–1940								9.8	4.1	13.6

The first case report, that of Mrs. B., brings out only too clearly the suddenness with which the factor of acidosis may alter the entire outlook in hyperparathyroidism. In this case, if the situation had not been immediately recognized and combated, an unhappy ending would have been the only reward for much work and skill. From a review of the literature it is difficult to estimate the frequency of acidosis as a complication. There is reason to believe, however, that it is relatively common and that it is associated with a high mortality.

In attempting to discover the causes of acidosis in such cases, one almost at once seeks an answer in the damaged kidney function displayed by so many of these patients. A large number of such patients suffer from nephrolithiasis, renal calcification, or tubular and glomerular nephritis. Excretory and blood tests frequently indicate a greatly diminished kidney function. Despite this fact but few of the case reports indicate that the patient suffers from acidosis; in fact, it would appear that excretory tests and the usual blood tests for renal function do not give any indication of the patient's liability to acidosis. In Case 1, renal excretion was impaired, blood nonprotein-nitrogen was slightly above normal, and the carbon dioxide combining power of the blood was lower than the usual level. Many another such patient, however, has exhibited more marked impairment of renal function and yet did not develop the complication of postoperative acidosis. Even patients with marked renal calcification have weathered operation successfully, and anuria or

suddenly increased malfunction has been the usual complications (7). It is interesting in this regard that Mrs. B. (Case 1) had the acidotic sequela but no tendency to anuria or further impairment of kidney function.

It seemed reasonable then to look elsewhere for an explanation of this variety of acidosis. From the data at hand, it would appear that shortly after operation the alkali reserve, as measured by the carbon dioxide combining power of the blood, became lowered markedly within a few hours. This must have come about through an alteration in the tissues or blood stream as no intestinal disturbance and no medication entered as a factor. The figures for nonprotein-nitrogen and the kidney function, as mentioned, did not hint at ordinary renal retention as an important factor. Examination of the changes in blood calcium and phosphorus after parathyroidectomy in hyperparathyroidism, and the effect of these changes on other factors in acid-base equilibrium, appears then the most logical source of information.

Before proceeding further into this, however, a brief summary of the recent ideas on the interfunctions of calcium, phosphorus, and parathormone is indicated. Helfet has recently clearly pictured parathormone controlling the blood inorganic phosphate level by stimulating the kidney to excrete more phosphates when they increase in the blood, and by mobilizing calcium from the bones to form salts which either hold the phosphates in the blood stream or allow their excretion by the kidney. Conversely, if parathormone is removed from the body, phosphate excretion is impaired and calcium is no longer mobilized from bone either to help its excretion or to hold it in the blood stream in a neutral form (5).

Fig. 6. Roentgenogram of pelvis and femora in Case 2, Mrs. McK., taken 2 months before parathyroidectomy.

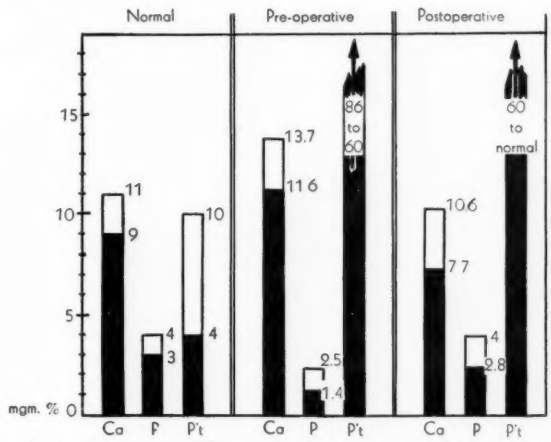

Fig. 7. Diagrammatic representation of serum calcium, phosphorus, and phosphatase figures in normal and in Case 2, Mrs. McK., before and after parathyroidectomy.

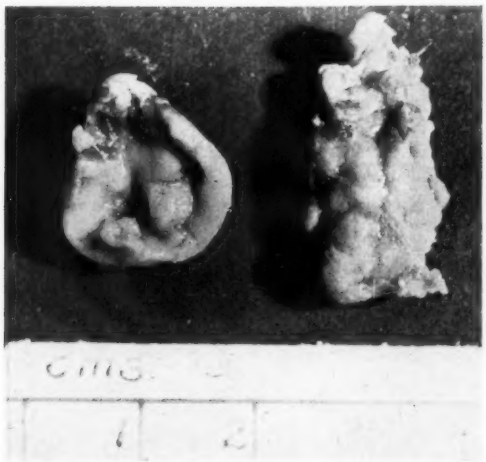

Fig. 8. Photograph of parathyroid adenoma in Case 2, Mrs. McK.

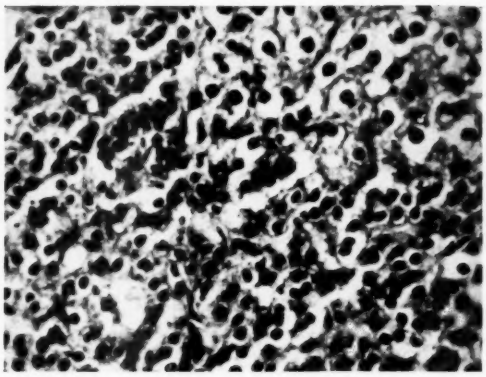

Fig. 9. Photomicrograph of section from parathyroid adenoma in Case 2, Mrs. McK.

With this in mind, it is further recalled that a kidney with impaired function tends to excrete certain acid radicals poorly, especially chlorides and sulphates. This seems to be especially true in hyperparathyroidism; and in this syndrome phosphates are also excreted with difficulty in spite of increased parathormone. Calcium, though certainly excreted in immense quantities by the kidney, tends to lodge in the soft tissues. Sodium is excreted freely (10).

The removal then of a hyperfunctioning parathyroid gland invites immediate chemical changes of great importance. With the loss of parathormone, phosphates no longer tend to be excreted by the kidney and increase, while the calcium that was mobilized from bone to take care of it no longer is freed. Therefore, the phosphates, sulphates, and chlorides, all acid radicals, tend to increase in the blood stream or in the tissues; while calcium, a base, is no longer withdrawn from the skeleton to the blood stream and the base sodium is excreted by the kidney. A process is thus set in motion that may prove sufficiently disturbing to the acid-base equilibrium to promote acidosis.

In Case 1, Mrs. B., some impairment of renal function was present before operation, carbon dioxide combining power was slightly down, calcium was increased in the blood stream, phosphorus was decreased in the blood stream. A few hours after operation, serum calcium was 12.6 milligram per cent, phosphorus 2.1 milligram per cent, and the patient was in good condition. But 10 hours after operation, when acidosis had suddenly developed, carbon dioxide combining power had fallen as low as 19 volumes per cent. A few hours after recovery from acidosis, serum calcium was 7.1 milligram per cent, phosphorus 3.1 milligram per cent. It seems reasonable to suppose that with the withdrawal of parathormone by operation, phosphates were retained in the body; while due to the kidney damage, sulphates and chlorides already tended to be retained. Thus acid radicals were increased while at the same time sodium was freely excreted, and calcium was retained in the body, not in the blood stream available to counteract acid radicals, but in bone. Thus basic radicals available to offset the increase in acid radicals were depleted leading to a depleted alkaline reserve and to acidosis.

The treatment of the acidosis by intravenous sodium bicarbonate was immediately and dramatically effective. The lowered carbon dioxide combining power changed to a normal level, indicating a supplementing of the alkaline reserves sufficient to offset the increased acid radicals. Besides being effective, sodium bicarbonate is a very safe agent to use to combat acidosis of this type, for the sodium if necessary is readily excreted by the

kidney while carbon dioxide is freely excreted by the lung. There is, therefore, no danger of overtreatment within reasonable limits.

A salt free diet, for a week or so before parathyroidectomy, would seem to be a logical preventative measure in these cases.

Before leaving the discussion of Case 1, it should be pointed out that the very mechanism here outlined that may lead to acidosis with rapidity may also lead to hypocalcemic tetany. When parathormone is no longer available after operation, calcium is no longer drawn from bone; and that calcium still in the blood stream is rapidly attached, diffusible calcium being rapidly used up. Thus tetany may appear with acidosis, render the patient's position precarious, and make a diagnosis of the exact condition even more difficult.

The second case reported here had diffuse rarefaction of the skeleton, but rarefaction was not evenly distributed. Bone cysts were present in the pelvis and femora but not in the other long bones. In the pelvis and femora, areas of calcium deposition were present. These areas in the x-ray film bore a strong resemblance to the changes seen in the roentgenogram in Paget's disease. However, the findings in the case and the postoperative course definitely established the diagnosis of hyperparathyroidism due to a hyperfunctioning parathyroid adenoma. Gutman and Parsons believe that this unusual picture is explained by the fact that hyperparathyroidism progresses often in phases. For a time much parathormone excretion results in much decalcification of bone; then decreased parathormone excretion brings about a period of recalcification of bone, usually in an uneven manner. The presence of areas of bone deposition together with bone rarefaction and bone cysts is thus accounted for.

The realization of such a possible variation in the bone pathology of hyperparathyroidism is important because such an x-ray picture as Mrs. McK. presented might lead one away from the true diagnosis. This would be especially true if by chance blood tests for calcium and phosphorus and phosphatase were taken at a time when parathormone activity was quiescent, rendering the tests within, or almost, within normal limits.

Fig. 10. Roentgenogram of pelvis and femora in Case 2, Mrs. McK., taken 4 months after parathyroidectomy.

SUMMARY

Two cases of hyperparathyroidism, due to the hyperactivity of parathyroid adenomas, have been reported. One emphasizes the importance of watching for postoperative acidosis, its grave dangers, and its effective treatment by intravenous sodium bicarbonate. It is also emphasized that acidosis and tetany may occur together. Cases must be carefully watched for both conditions, either of which may be fatal. An explanation is given for the occurrence of the acidosis following parathyroidectomy; briefly that acid radicals such as phosphates, sulphates, and chlorides tend to be retained in the blood stream while the base sodium is excreted freely by the kidneys and the base calcium is retained in the bones. A tendency for acid radicals to increase over basic radicals is thus present.

The other case illustrates how the skeletal changes shown in the x-ray film in hyperparathyroidism may closely resemble those of Paget's disease. It is pointed out that exacerbations and remissions of parathyroid activity could give this picture, bone being decalcified at one time and recalcified at another. Cases of Paget's disease should be carefully investigated with this circumstance in mind.

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THE CONTRACTILE RESPONSE OF THE HUMAN UTERUS TO POSTERIOR PITUITARY EXTRACT ADMINISTERED AT REGULAR INTERVALS DURING PREGNANCY

A Study of 32 Patients with the Lóránd Tocograph

DOUGLAS P. MURPHY, M.D., F.A.C.S., Philadelphia, Pennsylvania

THE Gynecean Hospital Institute of Gynecologic Research recently has undertaken an investigation of the contractions which the human uterus undergoes during pregnancy. This has included observations upon both the spontaneous ones (2), and upon those induced by the administration of posterior pituitary extract (3).

The latter study supplied information upon the general character of the response and on the effect of certain factors upon it. It told nothing, however, about the peculiarities of a given individual's total reaction throughout pregnancy, or in what manner the response of one person during gestation might differ from that of another. These deficiencies were due primarily to the small number of observations made upon any one patient as well as to certain variables inherent in the nature of the material. The present study was undertaken in order to throw light upon these subjects, and as far as can be determined no similar series of observations has been reported.

MATERIALS AND METHODS

Patients residing in the Sheltering Arms Home, Philadelphia, between June, 1939, and June, 1940, acted as subjects. This institution affords residence and prenatal care only, beginning at any time during pregnancy, for white and colored women who are illegitimately pregnant.

Each patient was brought under observation within 7 days of admission to the Home and was studied at weekly intervals thereafter. All records were made on the same day and hour of each week, when possible. Each observation period included a record of uterine contractions, and while these were being registered the patient received a dose of obstetrical pituitrin,[1] which was administered intramuscularly in the upper arm. The dose of pituitrin was the same each week during the entire period that the patient was under observation.

Doses of 1 minim were employed when the study was started. Since this amount failed to elicit a response in many instances, the dose was increased but was limited to 3 minims, because even this quantity caused discomfort to some patients.

The latest model tocograph (1) was used for the recording. This instrument, 3.0 by 8.0 by 6.5 centimeters in dimensions, is a mechanical device which registers upon a paper strip the change in the contour of the abdominal wall created by the change in contour of the underlying uterus when it contracts. The tocograph supplies data upon the incidence, strength, duration, and rhythmicity of the uterine movements. The technique of the recording was as follows: The patient rested upon her bed for 10 minutes. The tocograph was then placed upon the most prominent part of her abdomen in the midline, where it was secured with a belt, and spontaneous uterine activity was registered for a control period of 15 minutes. Without interrupting the recording, pituitrin was administered, the period of observation being continued for the following 30 minutes.

RESULTS

A series of 32 patients supplied the data forming the basis for the present report. The

From the Gynecean Hospital Institute of Gynecologic Research, Department of Obstetrics and Gynecology, University of Pennsylvania and the Sheltering Arms Home.

[1] Parke, Davis & Co.

TABLE I.—CONTRACTILE RESPONSE OF PREGNANT HUMAN UTERUS TO POSTERIOR PITUITARY EXTRACT

Weeks of gestation	Dosage in minims: 1.0				1.5				2.0									3.0													Totals: Treatments	+ Reactions: No.	+ Reactions: %
	Patient identification: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32			
16									−																								1	0	0
17									−																								1	0	0
18									−	−																							2	0	0
19									−	−								−															3	0	0
20									−	−								−															3	0	0
21									−	−								−															3	0	0
22									−	−								N.T.															2	0	0
23									−	−								−															3	0	0
24									−	−								−	−														4	0	0
25									−	−	−							−	+														5	1	20
26									+	−	−	−						−	N.T.														5	1	20
27									+	−	−	+						−	−	−													7	2	29
28					+				−	−	−	+						−	−	−	−												9	2	22
29					+				−	+	−	−						−	+	−	−	−	−	−									12	3	25
30	+	−			−				−	−	N.T.	−	−					+	+	−	−	N.T.	N.T.	−	+								13	4	31
31	−	−			−				−	+	−	N.P.	−					−	+	−	−	+	−	+	+	−	−						17	5	30
32	+	−			−				+	+	−	−	−					+	+	−	−	+	−	+	+	+	+	−	+	−	−		22	11	50
33	+	−			−				+	+	−	N.P.	−					+	+	N.T.	−	+	−	+	N.T.	−	+	−	+	−	+		19	10	53
34	−	−			−	+			−	+	−	N.P.	−	+				+	−	N.T.	−	N.T.	+	+	+	+	+	N.T.	+	+	+		20	12	60
35	−	−	−		−	+			+	+	−	+	−	+	+	+		+	+	N.T.	−	N.T.	−	+	+	+	+	−	+	+	+	+	26	17	65
36	−	+	−	−	N.T.	+	−	−	+	+	−	N.P.	−	+	+	−	−	+	−	N.T.	−	N.T.	+	+	+	+	+	−	+	+	+	+	28	16	57
37	+	−	−	−	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	−	N.T.	+	+	+	+	+	−	N.P.	+	+	+	30	22	73
38	+	+	−	−	−	N.T.	+	−	+	+	−	N.P.	−	+	+	+	N.T.	+	+	+	−	N.T.	+	+	+	+	+	N.T.	N.P.	+	−	+	26	18	69
39	+	+	+	−	−	+	−	−	+	+	−	N.P.	+	+	+	+	+	+	+	+	−	N.T.	+	+	+	+	+	N.P.	N.P.	+	+	+	28	22	79
40	+	+	−	−	+	−	−	+	+	+	−	N.P.	N.T.	N.T.	+	−	+	+	+	+	−	N.T.	−	N.P.	N.P.	+	+	+	N.P.	N.P.	+	+	24	16	66

(+) = Response
(−) = No response

(N.T.) = No tracing
(N.P.) = Tracing, but no pituitrin

Note: (a) Absence of any response on the part of patients 4 and 21. (b) Absence of response of remaining patients, prior to the twenty-fifth week of gestation. (c) Increasing frequency of response as pregnancy advances. (d) Greater response frequency following larger than the smaller doses of pituitrin.

frequency with which they exhibited contractile responses to pituitrin is shown in Table I, arranged according to the amount of drug administered and the time in gestation at which it was given. It will be observed that the patients who received 3 minims of the drug gave more responses than those who received less. The columns on the right of Table I also show that the frequency of the responses increased as pregnancy advanced.

There appeared to be differences in the incidence of response of various individuals to the drug. Of the 32 patients, 30 gave a response and 2 (patients 4 and 21, Table I) did not; 2 more (patients 3 and 13) gave only 1 response each.

TABLE II.—TIME BETWEEN TREATMENT AND CONTRACTILE RESPONSE

Weeks of gestation	No. of patients	No. of treatments	Average time—seconds
25	1	1	918
29	1	1	612
30	3	3	414± 22
31	4	4	855± 187
32	8	8	429± 81
33	7	7	370± 54
34	9	9	561± 40
35	10	10	385± 74
36	10	10	415± 45
37	11	11	293± 43
38	10	10	403± 87
39	11	11	260± 34
40	8	8	376± 40

Average interval in time between treatment and response of patients who received 3 minims of pituitary extract (Table I). Note shortening of interval as pregnancy advances.

TABLE III.—FREQUENCY OF CONTRACTIONS AFTER ADMINISTRATION OF POSTERIOR PITUITARY EXTRACT

Weeks of gestation	No. of treatments	Average No. of contractions per hour
25	1	21
26	1	25
27	2	18
28	2	12
29	2	25
30	4	17
31	6	20
32	9	27
33	8	24
34	11	19
35	12	16
36	13	22
37	20	19
38	17	19
39	18	17
40	10	16

Showing frequency of contractions after administration of pituitary extract, arranged according to duration of pregnancy. Note slowing of rate as pregnancy advances.

The character of the responses was quite uniform; only 1 patient (patient 29) exhibited an atypical response, and this showed a quantitative rather than a qualitative difference.

The patients who exhibited typical responses presented the following characteristics:

Subjective symptoms. Of the 313 treatments which were given, 68, or 22 per cent, produced either a feeling of tightness—56 treatments—or of actual pain. All of the latter reactions occurred after the thirty-first week of gestation.

Interval between treatment and objective response. It is of interest, first, to note that no patient experienced a response prior to the twenty-fifth week of gestation; second, that responses did not necessarily appear each week after they were first observed. The interval between treatment and response bore a direct relation to the duration of gestation. The intervals of the patients who received 3 minims of pituitary extract are shown in Table II, in relation to the duration of pregnancy. The nearer to labor the treatment was given, the shorter was the interval.

Character of typical contractions produced by pituitrin. The typical contractile response of the uterus to pituitrin consisted essentially of a series of clonic contractions. The frequency of these was determined for 136 of 162 treatment periods. The maximum was 37, minimum 3 and the mean 19 ± 6.6. The mean rate by weeks of gestation is summarized in Table III. It was found to be more variable and higher from the twenty-fifth to the thirty-sixth week than thereafter.

A good example of a typical response to pituitary extract is shown in Figure 2. It will be observed here, that although the contraction waves in general are very much alike, in many instances the first wave fails to disappear completely before the second one begins. This tendency toward a tetanic type of contraction, in connection with the initial part of the response, is very characteristic of the response of the pregnant uterus to pituitrin.

The contraction wave resulting from the administration of pituitrin resembles very much the waves which occur spontaneously at different times during pregnancy, but both differ from the waves which occur during the first stage of normal labor. It will be observed

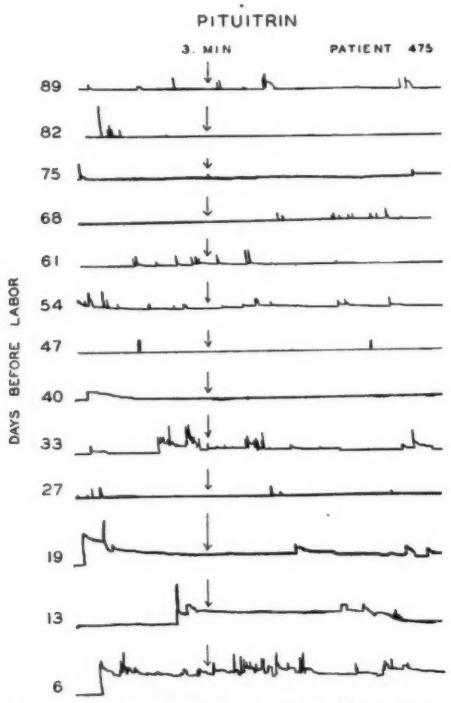

Fig. 1. Complete tocographic record of patient 21, Table I, who failed to exhibit a uterine contractile response to 3 minims of pituitrin at any time.

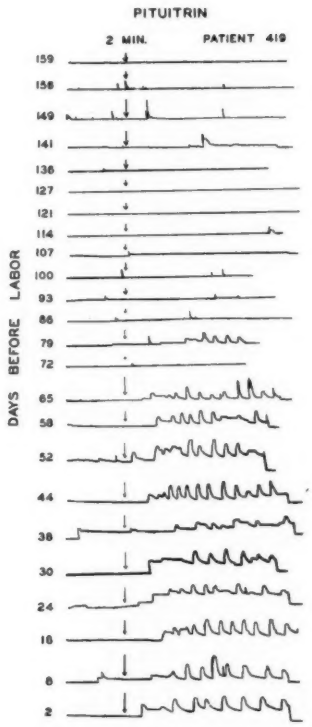

Fig. 2. Complete tocographic record of patient 10, Table I, whose uterine response to pituitrin was normal in character.

in the records shown in Figure 2, that the contractile phase of the waves following the administration of pituitrin is of short duration and therefore the rising arm of the wave is nearly vertical, whereas the descending arm is less steep. As pregnancy advances the total length of the wave increases but this is largely due to increase in the period of relaxation. During normal labor the rise of the wave is much slower than before labor, or following the administration of pituitrin. This marked difference in the pattern of the contraction following the administration of pituitrin, from that which occurs at the time of normal labor, may help to explain the difficulty encountered in attempting to induce labor by the use of oxytocic drugs.

The typical response and its relation to the tension of the uterine wall. As pregnancy advances the uterus undergoes not only intermittent contractions, but also changes in the tension of its wall which are independent of its contractions (2). As yet this characteristic of the pregnant uterus has been studied little.

We have been made conscious of these changes in tension because the use of the tocograph makes it possible to distinguish differences in tension which otherwise cannot be detected. The tension can be measured in the following manner: The instrument is placed upon the abdomen. If the uterus is not tense, the recording button sinks into the abdominal wall, and the recording lever continues undisturbed. A tense uterus, on the other hand, will force the button into the machine and raise the recording lever, in proportion to the tenseness of the underlying uterus. The distance traversed by the recording lever when the tocograph is placed upon the patient is a measure of the tenseness of the uterus.

The patients who experienced typical responses possessed soft uteri throughout pregnancy. Such was the case with the patient whose record is shown in Figure 3. Except for the tracing of this patient, made on the thirty-eighth day, the remaining ones indicate no increase in the tension of the uterus prior to treatment during the period covered by the present study.

The administration of pituitrin has two effects upon uterine activity. Early in pregnancy it inaugurates a series of intermittent contractions. Toward the end of pregnancy it increases the tension of the uterus at the same time that it induces rhythmic activity. This is well shown in Figure 2. With the disappearance of the intermittent contractions the increase in tension subsides. The tetanic effect observed in connection with the first contraction, as already mentioned, is related to the more prolonged period of increase in tension seen later in pregnancy.

Atypical response. Of the 30 patients who responded to the administration of pituitrin, only 1 gave an atypical response. This patient, not like the other 29 who exhibited uteri of low tension, possessed an extremely tense uterus. The tracings of this individual are presented in Figure 3. At the ends of each tracing of this patient is seen the level of the writing point before and after the tocograph was placed upon the abdomen. The level during the taking of the record is shown between them. The uterine tension which produced the high level of these tracings was considerably higher than that which is seen during normal labor, when an increase in tension is the rule.

As will be observed in the tracings shown in Figure 3, the immediate effect of pituitrin was to increase further the tension. This made the total tension so great that any impulses for the production of rhythmic activity were obscured since the uterus had already reached its maximum degree of contractility. Finally as the tension relaxed evidence of intermittent contractility appeared.

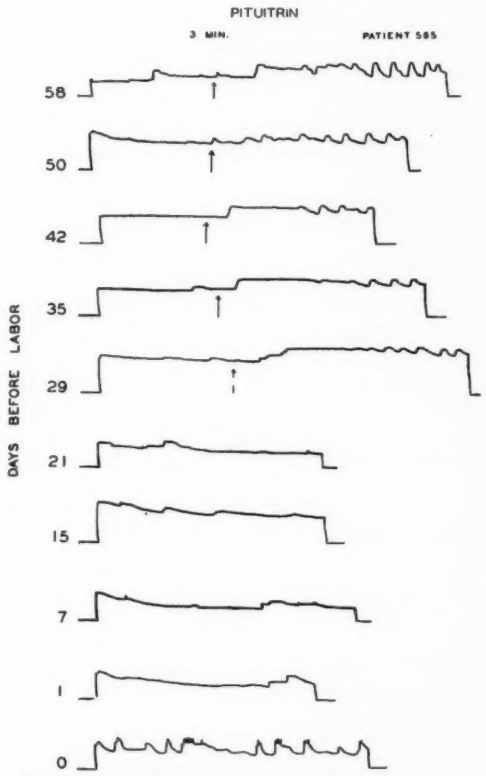

Fig. 3. Complete tocographic record of patient 29, Table I, who exhibited a high degree of uterine tension throughout pregnancy. Lowermost tracing made during labor. Tension of uterine wall measured in terms of level of middle of tracings above that at the ends. Note: (a) further increase in tension following treatment, and (b) temporary absence of rhythmic contractions during first part of period of increased tension.

OBSERVATIONS

The present study indicates that the uterine response of the individual to pituitary extract follows a pattern throughout pregnancy, and that the same pattern is followed by the majority of patients. The occasional patient may exhibit an atypical pattern. A comparison of the latter with the typical pattern suggests that the difference is essentially quantitative rather than qualitative.

The following considerations may help to explain the occurrence of atypical responses: There is reason to believe that the patient during pregnancy elaborates a posterior pituitary-like hormone. An individual may produce more or less of this substance than the average person. If she produces a normal

amount, a typical contractile response will follow the administration of pituitary extract. If the individual produces a subnormal amount, the response to pituitary extract will be either feeble or imperceptible. If she is elaborating too much of the hormone, the tension of her uterus will be unusually high; the administration of pituitrin in such a case will further increase the tension.

If the consideration mentioned has any foundation in fact, then this knowledge will aid in the proper use of pituitrin at the time of labor. It readily explains why certain patients fail to react to pituitrin, why most of them respond normally, and why a few experience tetanic spasms which may cause fetal death, or rupture of the uterus.

Unusual tension of the uterus can be detected by means of the tocograph. When it is found, it is a contraindication to the use of pituitrin. By using this knowledge we may be able largely to avoid the two dangers just mentioned.

SUMMARY AND CONCLUSIONS

Posterior pituitary extract was administered to 32 women at regular intervals during pregnancy while their uterine contractions were being registered with a Lóránd tocograph.

Two patients failed to experience a uterine response to the drug at any time during gestation; 29 experienced a characteristic reaction; and 1 exhibited an unusual response.

Patients who experienced typical responses exhibited the following characteristics: (1) a series of clonic contractions occurring at a rate of approximately 20 per hour; (2) onset of contractions after the twenty-fifth week of gestation; (3) a wide variation in the time in pregnancy at which they were first observed; (4) inconsistency with respect to appearance of contractions after they were first noted; (5) a shortening of the interval between treatment and onset of uterine response as pregnancy advanced; (6) a slowing of the contraction rate as pregnancy advanced; (7) no unusual tension of the uterine wall before treatment.

An atypical response was observed in a patient possessing an extreme degree of tension of the uterine wall. The pretreatment tension was increased by pituitrin, resulting in a prolonged, intensely painful spasm.

From the above observations the following conclusions are reached:

1. Patients vary widely in their uterine response to pituitrin during pregnancy.

2. The contraction pattern depends largely upon the tension of the uterine wall.

3. An evaluation of the tension of the uterine wall before the administration of pituitrin at the time of labor may assist in the avoidance of accidents which result from prolonged and severe tetanic spasm.

The author is indebted to Dr. Dorothy L. Ashton for the privilege of studying the patients upon her service at the Sheltering Arms Home.

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THE BACTERIAL CONTENT OF AIR IN THE OPERATING ROOMS

THURMAN B. RICE, M.D., LYLE A. WEED, Ph.D., M.D., HAROLD RAIDT, M.S.
Indianapolis, Indiana

UP to the period of about 1865 many people held the view that what we now recognize as infection was a spontaneous process on the part of tissues. The development of minute living forms in dead tissue of plant or animal origin was referred to as spontaneous generation. The belief that certain of these minute forms were related to, if not the cause of, infection stimulated critical minded workers to study the basic problems of fermentation and putrefaction. The demonstration of the minute particles suspended in air as being related to decomposition was one of the contributions by Tyndall, a mathematician and physicist. By means of a crude box, through which a beam of light could be passed, he proved that "spontaneous generation" did not take place when all the particles within had settled out so that the beam of light was no longer visible from the side. At this early date Tyndall was actually using a beam of light to analyze air for the presence or absence of bacteria-laden particles. Stimulated by research on the bacterial nature of fermentation, putrefaction, and infection, Lister conceived the idea of operating upon patients in an atmosphere of a solution of phenol to prevent infection of the wound from the contaminating air particles.

Since that time the development of surface asepsis and antisepsis relative to surgery has occupied the attention of many investigators to such an extent that many other possibilities have been overlooked as a source of infection. Asepsis was developed so that today instruments are scrupulously cleaned and sterilized with heat, the operator is clothed in a sterile uniform, a mask is placed over the nose and mouth with the intent of preventing bacteria therefrom coming in contact with the wound, the patient is carefully draped with sterile linen, so that only the area involved in the operation is left exposed. Antisepsis was developed so that potent germicides are used in the attempt to sterilize or at least disinfect the skin of the patient at the site of operation. In more recent times, many investigators, particularly Meleney (6, 7) and Hart (1, 2, 3, 4), have called the attention of surgeons to the air as a possible source of infection in otherwise "clean" surgical wounds. Meleney (6) reported a 9 year study of operative infections and, after carefully considering the various sources, listed them in order of importance as follows: (a) nose and throat of operators, (b) hands of the operator, (c) skin of the patient, (d) air of the operating room, (e) instruments and materials. By exposing Petri dishes in the operating room he found ten times as many organisms on operative days as on non-operative days. However, no data were presented to substantiate this statement. He emphasized the fact that the study in itself made the staff "infection-conscious" and care of each detail led to a reduction in the incidence of infection. Hart (1), after studying the source of infection in operated wounds, says, "as soon as a Petri dish of blood agar was exposed to the air in the operating room the source of our infections was evident. Invariably large numbers of organisms, predominately staphylococci (albus and aureus), settled out of the air. . . . Cultures from the walls and ceilings showed Staphylococci to be present." He was of the opinion (2) that air conditioning greatly reduced the bacterial content of the air. Later he (3) presented data to demonstrate that the number of pathogenic bacteria in the air of a room increases directly with the number of occupants, although we cannot agree that these data may properly be so interpreted. More recently he (4) has presented data (obtained by exposing one blood agar plate per week for a period of one year) and has inter-

From the Department of Bacteriology, Indiana University Medical Center.

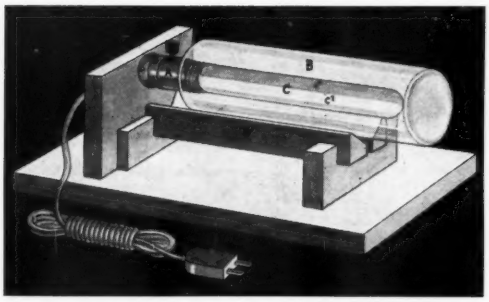

Fig. 1. Device used for examining the centrifuge tube, *B*; *A*, electric switch; *C*, illuminating bulb—C^1, portion covered with white paint to reduce glare, C^2, portion unpainted; *D*, support.

preted them as demonstrating a relationship between the number of bacteria in the air and the incidence of wound healing. As a result of emphasis on the air as a possible source of infection in the so-called "clean" operative wound, ultra violet lamps are now available to sterilize (?) the air—especially that immediately over the operative field. Recent work by Wells (13), however, suggests that, in such a system, there are inherent defects which definitely limit its usefulness for this purpose.

PURPOSE OF THE INVESTIGATION

Because of the occasional infection of "clean" surgical wounds in our local hospitals we undertook to study their possible and probable sources. Since the literature contains so much indirect evidence that such bacteria in the wounds come from the air and thus indirectly from the operating personnel, we felt work along this line should constitute the chief phase of our investigation, at least in the beginning. We, therefore, proposed to study thoroughly the bacterial flora in our own operating rooms, keeping as complete and accurate records as possible concerning the various activities in the room during a working day which we considered might influence the bacterial population of the air. In order to have complete, detailed information, it was proposed that chronological records should be kept of the number of people in the room; whether they wore masks; whether they were nurses, doctors, or students; when the nurse started preparing for the operation and how much time it required and whether there was any undue activity in such preparation; the duration and kind of operation and details relative to cleaning the room after the operation. All these factors were then to be considered in connection with the bacteriological data in order to interpret completely the results of each day's experiment. In other words, it was proposed to study first hand and by direct fashion the cause-effect relationship between the number of people and their activity in a room and the bacterial flora of that room. On the basis of such data we would then be in a position to decide in a logical fashion upon the proper method for correcting the procedure and thus minimize the incidence of infections. At the same time additional investigations were started to determine other possible sources of infection besides the air. Data bearing on these will be presented later.

METHODS USED

1. The Petri plate method was used throughout the course of the investigation, partly because it is a commonly accepted procedure, and partly to obtain sufficient data to show the errors of such technique. The Petri plates were the standard 100 millimeter diameter size, containing blood agar of the following composition: Difco nutrient broth, 2 per cent agar agar, 6 per cent citrated human blood. The plates were incubated aerobically at 37 degrees C. for 48 hours and examined on a Quebec colony counter. In order to have fair sampling of the air and at the same time not interfere with the surgical procedures, it was decided to expose routinely four such plates, each time for a period of one hour, a fifth plate being placed on the operating table when it was not otherwise in use. The distribution of the plates is shown in Figure 2. The plan was to expose the plates at various times of the day in such a fashion that the data so obtained might be compared with the data obtained from the Wells' air centrifuge. Sets of plates were therefore exposed (as regularly as possible) from 7 to 8 a.m., 9 to 10 a.m., 11 to 12 a.m., 1 to 2 p.m., and 3 to 4 p.m., thus covering the period of activity in the operating room. (This required the exposure of 20 to 25 plates per day as compared with one per

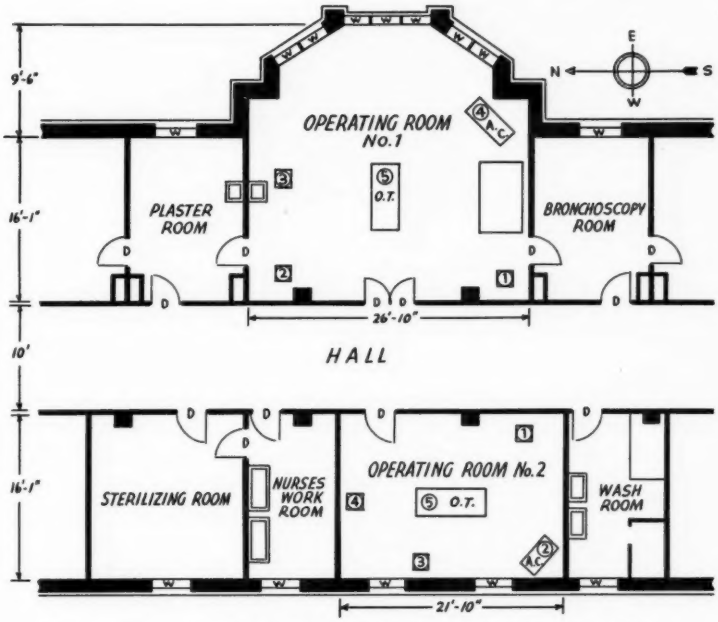

Fig. 2. Arrangement of operating rooms showing distribution of Petri dishes.

day as used by some investigators). Samples were usually collected on alternate days of the week (Monday, Wednesday, and Friday) during the first part of the investigation (November to February), and on Tuesday, Thursday, and Saturday during the remainder of the time. Sunday samples were collected at random throughout the winter and summer months.

2. The Wells' international air centrifuge (11) was used to collect periodic samples at hour intervals throughout the day, usually from 8 a.m. to 4 p.m. On specified occasions samples were collected at half hour intervals. The instrument used was operated to draw 10 cubic feet in 6.5 minutes. Duplicate samples were always collected. The medium used was blood agar, kept fluid in a sterile thermos bottle. Experience soon demonstrated that if the medium was kept longer than approximately 3 hours the blood began to turn brown, making the examination of the tubes difficult because of the opacity. The medium was also unsatisfactory from the point of view of hemolysis (alpha or beta). The tubes were examined on the illuminating device shown in Figure 1, in which *A* represents the electric switch, *B* the centrifuge tube to be examined, carried on support *D*, *C* the illuminating bulb with portion C^1 covered with a white paint to reduce glare and portion C^2 left unpainted. The bulb is a 25 watt inside frosted Mazda lamp manufactured by Westinghouse. Dr. Kenneth MacDonald, University of Iowa, suggested the original form, of which this is a modification. Centrifuge samples were collected on the same days the Petri plates were exposed. The tubes were incubated 48 hours at 37 degrees C. aerobically. The samples from outside the operating room on the second floor were obtained by suspending the centrifuge on a rope hanging from the third floor window immediately above the operating room and pushing the instrument away from the wall by means of a wooden pole. The samples inside the operating room were taken with the instrument placed on a table 3 feet high, this being not only a convenient height, but also at a level comparable to the Petri plates and to that of the patient on the operating table.

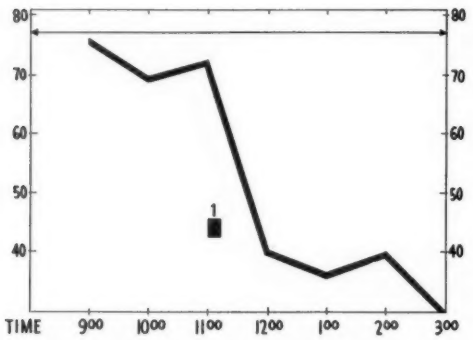

Fig. 3. Hourly distribution of bacteria in 10 cubic feet of air, door open all day. Riley operating room 1. December 4, 1939.

The original plan was to collect samples from directly over the operative field by means of a sterile rubber tube (1 inch inside diameter) extending from the patient to the intake of the centrifuge. It should thus be possible to examine the air in the immediate vicinity of the operative field directly in place of indirectly by examining air from other parts of the room. As a preliminary experiment to prove the system would operate, a 10 foot piece of tubing, 1 inch inside diameter, was adapted to the intake of the air centrifuge. The opposite end of the tubing was then placed at different levels of the room and duplicate 10 cubic feet air samples collected. These samples were then compared with the air samples collected without the rubber tubing in place. Only an occasional colony developed in the tubes used to collect air drawn through the rubber tubing, whereas the counts ranged from 65 to 80 in the tubes used to collect samples directly, i.e., without the rubber tubing. The experiment was repeated several times with similar results, indicating that such a procedure could not be used for the proposed experiments in the operating room.

3. Dust analyses were made on a few occasions with the hope of obtaining data which might be correlated with the bacteriological findings. For this purpose the standard impingers for dust analysis were used, with a rate of flow of 1 cubic foot per minute. Samples were collected for periods of 1 hour each at intervals corresponding to the exposure of the Petri plates. Portions of the samples were examined in the standard counting chamber and calculations made to determine the number of particles per cubic foot of air.[1]

4. Humidity determinations were made by means of the sling psychrometer at hourly intervals to correspond as closely as possible with the rest of the samples collected on those days.

5. Temperature determinations during the winter and spring months were automatically controlled, and since there appeared to be no demonstrable relation between temperature and the bacterial content of the air, such determinations were not continued throughout the full period of investigation.

6. Complete data were recorded concerning the number of people present, the amount and kind of activity in the operating room, whether the windows were open and if so whether there was a demonstrable breeze, and all other minor conditions which might possibly be considered as influencing the bacterial flora.

7. We have tried the apparatus described by Hollander and Dalla Valle, but found it unsatisfactory because we were not able to obtain results which were either uniform or comparable to any other procedure available.

8. Operating room technique: As a general rule, anyone entering the operating room wore a mask over the nose and mouth if an operation was being performed. At all other times no mask regulation was enforced. During warm days in the fall and spring seasons it was not uncommon to have at least one window partially open, even during an operation. In the late spring and summer days the windows were quite uniformly open and at times (especially on uncomfortably hot, humid days) an electric fan placed on the floor was operated to add to the comfort of the operating personnel. During the summer months, as has been the practice in past years, the doors to the operating rooms were commonly, though not always, allowed to remain open during operations.

9. In order that the reader may properly interpret the various problems relative to

[1]The dust analyses and humidity determinations were made by J. F. Keppler and J. S. Wiley under the supervision of Dr. Louis W. Spolyar, director of the Bureau of Industrial Hygiene, Indiana State Board of Health, and we take this opportunity to express our appreciation for such assistance.

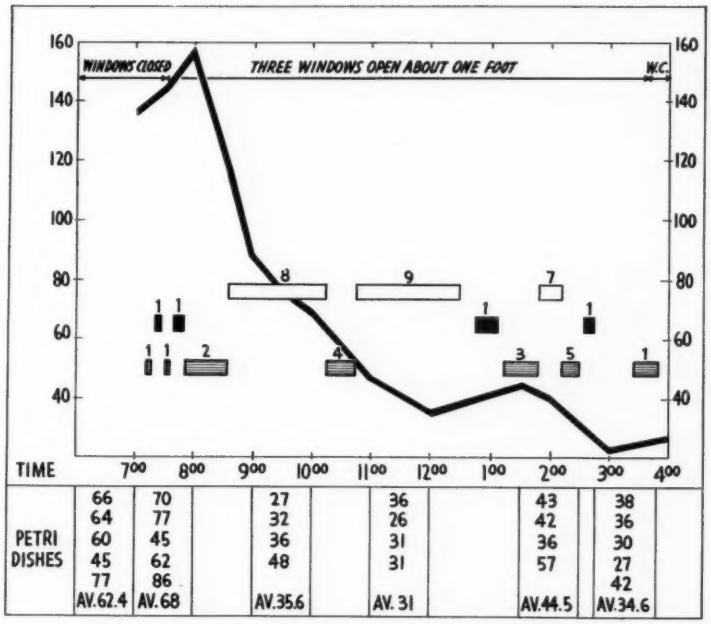

Fig. 4. Hourly distribution of bacteria in 10 cubic feet of air, Riley operating room 1, August 22, 1940. The white rectangles indicate period of operation; the black rectangles, janitor service; the horizontal lined rectangles, preoperative and postoperative activities. The numerals above the rectangular areas indicate the number of people in the room.

sampling the air, as well as understand the various factors which may influence the experiments, a diagram is presented in Figure 2 to show the size, shape, and relative positions of two of the operating rooms where the major part of the data was obtained. The positions of the exposed Petri dishes are clearly indicated by the encircled arabic numerals. The numbers given correspond to the positions of the data given in Figures 4 to 8 inclusive, the top figure in the chart being represented by the position number *1*, the second by number *2*, etc. This investigation covered a period of time extending from late November, 1939, to September 13, 1940, during which time the bacterial content of the air in the operating rooms was determined on 85 separate days. The investigation involved the examination of over 1,500 samples taken with the air centrifuge and over 1,800 Petri dishes were exposed.

ANALYSIS OF DATA

In the early part of the investigation, samples of air were collected by the air centrifuge method on the assumption that a direct relationship existed between the number of bacteria laden particles in the air and the number of persons in the operating room. Consequently, most of the samples were obtained during the working day. Analyses of the data as they were accumulated indicated very clearly that the bacterial count was about twice as high in the morning as in the afternoon. This was to be expected since all of the operations had been done in the morning. As controls, samples were collected on days when there were no operations and data of the type represented in Figure 3 were obtained. Data of this type were obtained on several occasions and it soon became apparent that the general distribution of bacteria in the air of the operating room for any given day varied in

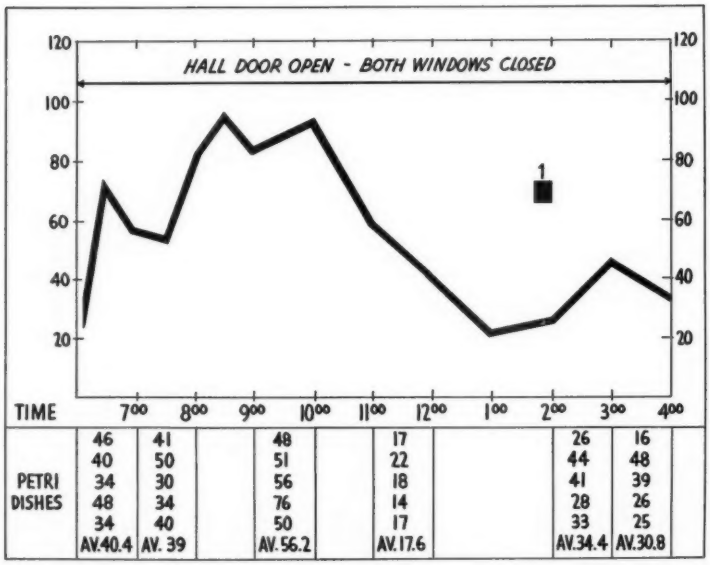

Fig. 5. Hourly distribution of bacteria in 10 cubic feet of air, Riley operating room 2, April 26, 1940.

this fashion, irrespective of activity, number of persons, or whether operations were performed. Figure 4 shows very clearly that the high count is not dependent upon either number or kind of operations, number of people in a room, or the nature of the activity. During the first operation 8 people were present in the room, during which time the count dropped to about half what it was before the operation. During the second operation the count continued to drop in spite of the presence of 9 people. From the data represented in this particular chart it is impossible to determine whether the high morning count is due to the cleaning and pre-operative activity or to some other factor. The continued low count in the afternoon when pre-operative and postoperative activity is just as great suggests that some other explanation should be sought. In the light of other information now available, it may be that the sudden drop at 9 o'clock is due to the opening of the windows. While the averages of the counts obtained by the Petri dish method follow a general trend simulating the air centrifuge data, examination of the individual counts reveals a marked variation from hour to hour for a given position and from one position to another for a given hour.

In an attempt to determine the cause of the "high morning-low afternoon" counts data were kept relative to every possible related factor. At first the radiators were considered, the assumption being the early morning heat would set up convection currents and resuspend particles which would slowly settle out for several hours. It was soon discovered that the temperature in the rooms remains constant in the fall, winter, and spring months (when the work was just well started) and convection currents were just as great in the afternoon as in the morning. The effect of the ceiling lights and the operating lamps as possibly influencing the counts was soon ruled out by obtaining similar data on non-operative days when the lights were not being used.

Since operating room 1 is on the east side of the building and has a large bay window, the possibility of the sunlight charging the air particles to keep them in suspension was considered. This was shown not to be the case by obtaining similar data from operating room 2 which is just across the hall from room 1 and

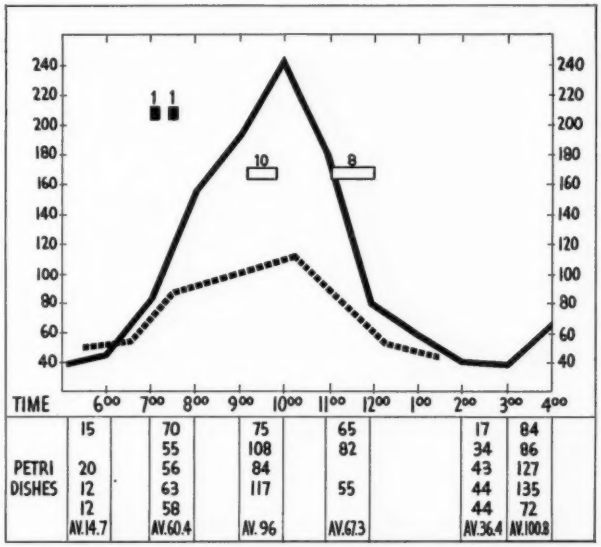

Fig. 6. Hourly distribution of bacteria in 10 cubic feet of air, March 28, 1940, Riley operating room 2, black line; hall outside operating room, interrupted line.

on the west side of the building. If sunlight were related to the phenomenon of "high morning-low afternoon" counts in operating room 1 then the reverse should be the case in operating room 2, i.e., the counts should then show "low morning-high afternoon" distribution. Such was found not to be the case. In bacteriological analysis of the air of 3 operating rooms in 2 buildings on two different levels (second floor and fifth floor) similar hourly distributions have been found to prevail as a general condition, yet one operating room looks north, one east, and one west.

Since smoke investigations revealed air currents entering operating room 2 via the transom, we considered the possibility of dust from the traffic in the hallway as possibly being the source of the organisms. Samples were therefore collected early in the morning and it was soon found (Fig. 5) that the bacterial count is low as late as 6 a.m. and then begins to rise rapidly during the next 2 or 3 hours. Apparently this was the source of the high bacterial count in the morning samples since the activity in the hallway is greatly reduced by approximately 11 a.m. In order to prove the validity of this hypothesis dust counts were made in the hallway and in the operating room at the same time bacterial samples were collected. The dust counts plotted in millions per cubic foot against time followed the same type of distribution as the bacterial counts shown in Figure 6; i.e., the dust counts were lower in the hallway than in the operating room. While such data are entirely opposite to those expected, we repeated them enough to believe they represented actual existing conditions.

Since data obtained earlier in the summer indicated that the bacterial content of the air in the operating room was lower with the windows open samples were collected outside the windows on certain days to see how they would compare with those taken inside. Since only one air centrifuge was available and since insects came into the room when the screens were removed, only a few days were suitable for collecting such comparable data. An example of such data is shown in Figure 7. This shows the low count in the air 6 feet outside the window on a still day as contrasted with the high count inside the operating room. It

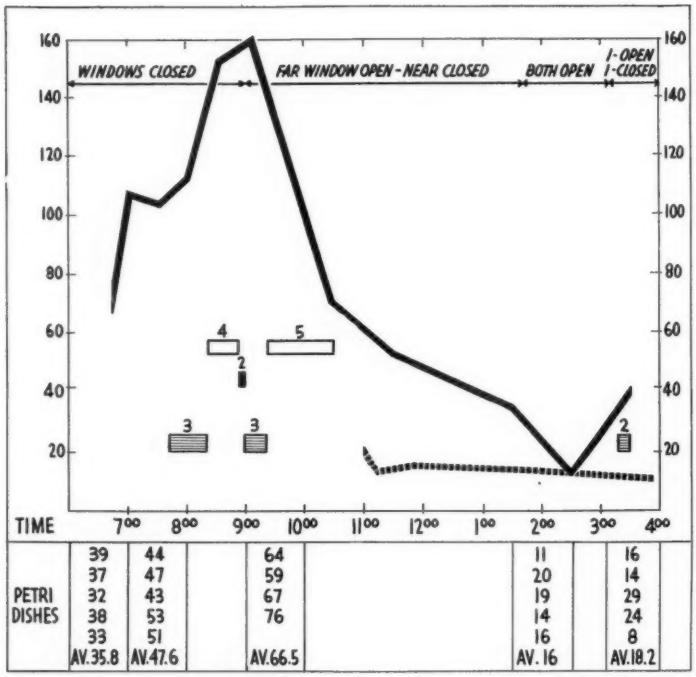

Fig. 7. Hourly distribution of bacteria in 10 cubic feet of air, August 20, 1940, in Riley operating room 2, black line; outside window, interrupted line.

also shows that during an operation when 5 people are working, with the windows open there was a rapid decrease in the bacterial content. Figure 7 also shows that the early count is lower than "mid-morning" and that the trend is rapidly upward before there is any activity in the room. Figure 4 more graphically demonstrates the effect of opening the windows because in it the rapid decline is noted at 9 a.m. when the tendency normally is to be at a peak whereas in Figure 7 the decline begins about 10:30 which has been found sometimes to occur normally.

It would be erroneous to present data showing only uniformly smooth curves to represent the bacterial population in the air of the operating room. While the data for a given day are usually represented by relatively smooth curves as herewith shown, there were days when the variations were quite marked as shown in Figure 8. There was no known activity within the room or adjoining hallway or climatic conditions outside (e.g., winds) which could logically account for this fluctuation. Attention is called to the counts on the Petri dishes exposed for the two periods 7:30 to 8:30 and 9:00 to 10:00; there being wide differences within each group exposed at a given time, the two averages, however, being identical but differing greatly from the data obtained by the air centrifuge.

Since it is customary in many hospitals to postpone certain elective major operations until summer, it was of interest to analyze the data on bacterial content of the air in the operating room according to seasons. In order to show the variations it was decided to use months in place of seasons since the latter vary considerably. Probably it would have been better to have used weekly averages but the data available would hardly justify such analysis. An examination of Figure 9 shows very clearly the uniform tendency for the bacterial count to be high during the morning

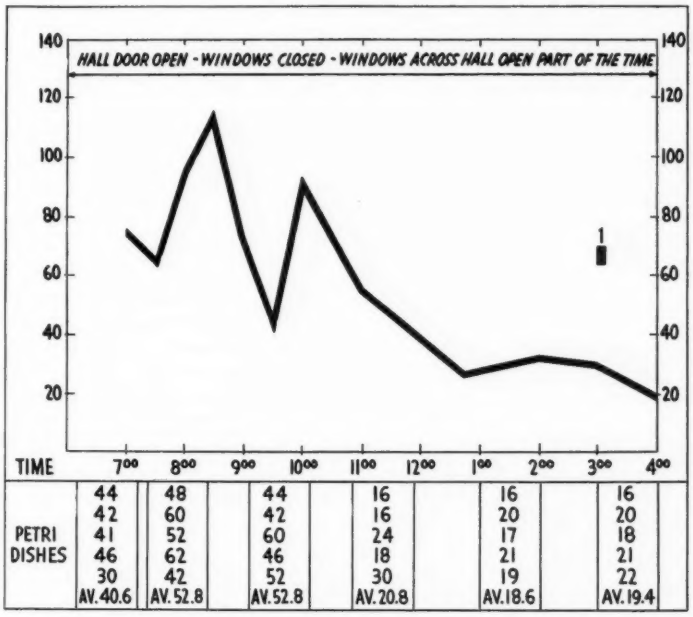

Fig. 8. Hourly distribution of bacteria in 10 cubic feet of air, August 2, 1940, Riley operating room 2.

hours and low in the afternoon, irrespective of the month; one exception being in July when the variations are irregular. Not enough data were available for the month of May to be statistically important although those available follow the same general trend as for April and June. It is significant that from an examination of the data in Figure 9 alone one might justifiably conclude that the high morning counts were due to the increased activity relative to operations performed at that time but it has been demonstrated repeatedly that there is no real cause-effect relationship between such operations and the magnitude of the count. It is emphasized that the data for the averages represented in Figure 9 were obtained under a variety of conditions but which nevertheless represented the type of conditions under which the operations were performed, i.e., windows open and closed, doors open and closed, sometimes with one, few, or several people in the room.

In order to demonstrate the manner in which the count varies from month to month for a given hour of examination the data were plotted against the months as abscissa as shown in Figure 10.

EVALUATION OF STUDY

While we have pointed out that a bacteriological examination of the air by means of exposing Petri dishes is not a reliable procedure, it would still appear that the falling bacteria-laden particles and not the suspended droplet nuclei would be the ones important from the standpoint of infecting exposed wounds. With such variations as we encountered in routine examination, however, it is obvious that the procedure cannot yield reliable data even from the standpoint of wound infections. Had we exposed at the hourly intervals only a single Petri dish as some have done, the results would have varied significantly according to the particular location designated for the exposure. In fact the data by Hart (3) show just such a variation. We can only speculate as to what the data would have shown had we collected air samples with four or five air cen-

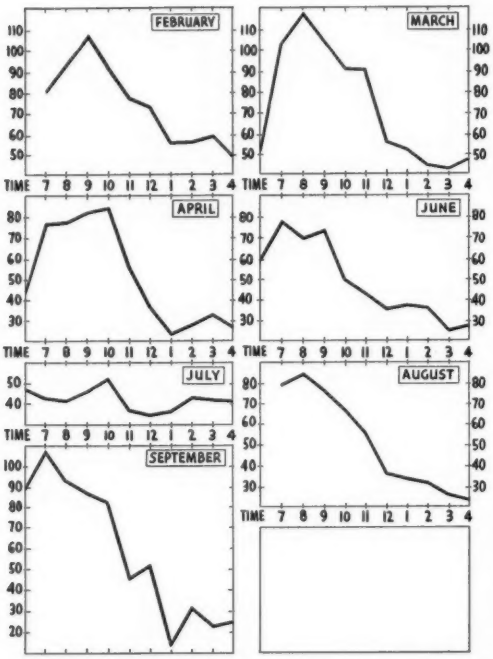

Fig. 9. Average hourly number of colonies from 10 cubic feet of air, during several months in 1940, Riley operating room 2.

trifuges located at the various places in the room corresponding to the exposed Petri plates. Irrespective of the location of exposure, the Petri dish counts tend to be much higher in the morning than in the afternoon. Without further consideration, one would naturally attempt to correlate this with the amount of activity, since nearly all the operations are performed in the morning. However, when one considers all the data for a given day it becomes quite evident that a cause-effect relationship does not exist between the operative procedures and the high bacterial count. While Hart (3) interpreted his data as suggesting such a relationship, we do not feel that they warrant such an interpretation. We recognize the value of statistical analyses but a careful examination of the data obtained for a given day will not allow a deduction that the number of contaminated particles (large enough to fall or small enough to remain suspended) in the air of the operating room are the result of or proportional to either the number of people or the amount of activity in the room. In this connection we would refer to data obtained on a day when a bilateral radical mastoidectomy was performed between 1:30 and 3:30 in the afternoon. The air samples taken during the operation contained no more organisms than those taken before or after, and less than those taken during the morning.

If the infected particles in the air do not come from the occupants, either directly or indirectly by resuspending dust particles, one must find some other suitable explanation of their presence. We therefore studied the air currents in the operating room by means of smoke and found that while there were no air currents coming in from the windows, there was a marked flow of air into the room from the hallway via the transom. In view of the extensive traffic in the hall we studied the bacterial content of the air in the hallway on the half hour and in the operating room on the hour (Fig. 6). The data obtained show that there are fewer bacteria-laden particles in the hallway than in the operating room for a given period. This is especially significant since patients, nurses, doctors, students, and ward help moved about freely in the hallway without masks. Even in the winter months, contrary to current belief, we found the bacterial content of the air lower in the hallway than in the operating room. However, the count was higher in the morning than in the afternoon, simulating qualitatively the hourly distribution found in the operating room. Correlated with the bacteriological examinations were the dust determinations which showed the same type of hourly distribution but with fewer particles in the hallway. It should be emphasized that the "high morning-low afternoon" counts are obtained at various seasons of the year and on nonoperative days as well as on operative days. Because of the latter we secured the cooperation of the housekeeping department and eliminated all cleaning on certain days, but the general distribution of infected particles remained the same. The production of convection currents from the radiators being heated in the morning was ruled out because the radiators are thermostatically controlled

and the temperature in the fall, winter, and spring months does not vary more than 1 to 2 degrees—day or night. The effect of sunlight on the air was considered as possibly being related to the peculiar distribution, but this hardly seems plausible since the condition existed in each of the three operating rooms; one with a north, one with an east, and the other with a west exposure. Again, contrary to current opinion and what one would ordinarily expect, the "high morning-low afternoon" type of distribution is lost if the windows are open. It is true that the Petri dishes sometimes indicated a high count immediately on opening the windows, probably due to a sudden inrush of air carrying dust from the window sill, but after a few minutes the air flora, as measured by the air centrifuge, dropped markedly and rapidly. This fact suggested that the organisms in the air of the operating room were coming from the occupants, but we believe that the rest of our data not only do not support the idea, but disprove it to a great extent, or, we believe, entirely, since samples collected during the time of operation and while the amount of activity was at its height showed no increase over those taken at other times and samples taken on nonoperative days showed the same general distribution as those taken on operative days. Under these circumstances, if activity in the room increases the bacterial count by the Petri dish method, there should be a similar change in the counts of the air centrifuge method when the counts are taken simultaneously. It further suggests that the air in the operating room should be changed frequently to reduce the number of bacteria in the air. Since one has no control over the outside air it should preferably be filtered to make it free of bacteria, and warmed in the winter months. This is certainly not a new idea, but the basis for the suggestion we believe is new.

If the bacteria in the air are not directly related to the incidence of wound infection the natural question is: What else might be the source of the organisms? The following sources have been mentioned by other investigators: perforated gloves, nonsterile operative site, nonsterile equipment (instruments, sutures, ligatures, and drains) and finally, organisms

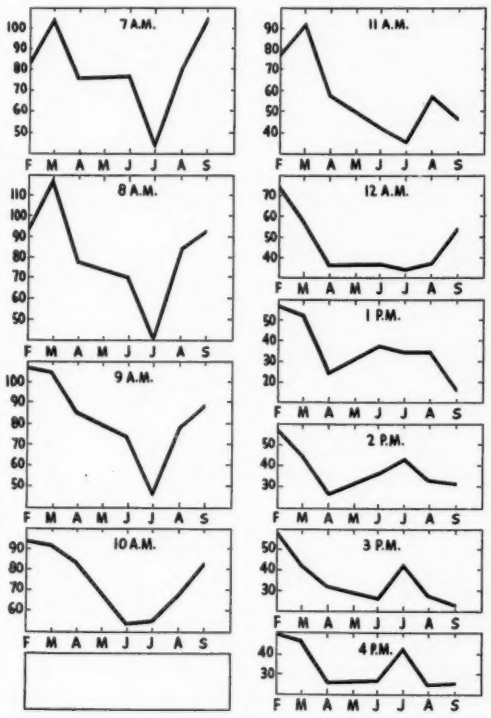

Fig. 10. Hourly averages of bacteria in 10 cubic feet of air by months, Riley operating room 2.

which are present in the patient's own tissues. It is neither logical nor probable that any one factor is all important as a source of infection (unless it be the patient's tissues). It is necessary, however, to investigate all possible sources in order that each one may be properly evaluated. Other phases of the work are in progress and the data obtained to date support the suggestion that a clean wound may be infected by bacteria coming from perforated gloves, nonsterile equipment, and the patient's own tissues.

The elimination of organisms from the nose and throat has been given much consideration in the past and is the basis of the commonly used practice of wearing a mask over the nose and mouth during surgical operations. Recently there have appeared some very graphic demonstrations of the number of bacteria possibly thrown into the atmos-

phere during coughing, sneezing, and talking (9, 14). To our knowledge, however, there has been no demonstration that bacteria are disseminated into the atmosphere during the process of normal respiration. In fact, our own experience (unpublished) has been that bacteria are not eliminated during either quiet or forced expiration, so long as there are no large droplets of saliva expelled, such as occur with talking, sneezing, and coughing. In support of this idea is the work of Rooks, showing that the nasal passages actually remove large numbers of organisms from the inspired air. Wells (12) has shown that droplets of 0.1 millimeter in diameter or larger fall very rapidly. As far as possible infection of clean surgical wounds in the operating room is concerned, it would appear that these would be much more important than the droplet nuclei. Since apparently no reliable data are available on the efficiency of the various types of commonly used masks, we can only conjecture as to the real surgical importance of bacteria coming from the nose and mouth of the operating personnel. This problem is under investigation at present.

SUMMARY AND CONCLUSIONS

1. Data are presented to show the hourly fluctuations in the bacterial content of the air in three separate operating rooms in current use at the Medical Center. The samples were collected from three operating rooms on 85 separate days, and involved over 1,500 determinations with the Wells air centrifuge and exposure of over 1,800 Petri dishes. The period of examination covered winter, spring, and summer months.

2. Irrespective of the season of year, the bacterial content of the air during morning hours (8:00–11:00) was commonly twice that found during the afternoon. Such high morning counts were demonstrated not to result from the amount or kind of activity nor the number of occupants in the operating room. No satisfactory explanation for this type of distribution has been found.

3. The bacterial content of the air was found to be slightly lower during the summer months than during the winter, but only significantly so when the windows were open.

4. The Petri dish method, in our experience, was not a satisfactory method for determining the bacterial content of the air. While there were certain disadvantages in using the Wells air centrifuge for this purpose, we believe it the best method available for large volumes of work.

5. While the bacterial content of the air in the operating room may occasionally be a source of infection for the clean surgical wound, we believe its importance has been greatly overemphasized.

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THE PROBLEM OF THE TREATMENT OF PERITONITIS

Preliminary Report

CHARLES E. REA, M.D., Minneapolis, Minnesota

PERITONITIS is the chief complication that surgeons dread in abdominal surgery. Much experimental work has been done on the production and prevention of peritonitis in animals, with attempts to correlate these findings with the prevention of peritonitis in human beings. The purpose of this paper is to compare the relative efficacy of certain substances in preventing peritonitis in rabbits.

In general, peritoneal protection may be produced by five methods: (1) intraperitoneal use of certain drugs and antiseptics; (2) introduction of a vaccine into the peritoneal cavity, producing a general immunity in which the peritoneum shares—true immune process; (3) antibacterial sera—passive immunity; (4) local protection of the peritoneum attributable to a local hyperleucocytosis and afforded by the intraperitoneal introduction of any number of vaccines and other substances; (5) use of agents, such as deep x-ray therapy.

INTRAPERITONEAL USE OF CERTAIN DRUGS AND ANTISEPTICS

While certain chemicals may kill organisms *in vitro*, when introduced into the peritoneal cavity, they often cause more irritation than good. Recently the use of sulfanilamide has enjoyed some popularity. Garlock and Seley believe the incidence of peritonitis following operations on the colon to be decreased if sulfanilamide is given for 3 days preceding operation and for several days thereafter. Ladd, Botsford, and Curnen state that the high mortality rate in primary peritonitis in infants and children can be markedly reduced by early operation and drainage followed by adequate treatment with sulfanilamide in the streptococcal group and type-specific serum in the pneumococcal group. Ravdin and his coworkers found that the mortality in appendicitis with peritonitis was lowered from 1.4 to 0.4 per cent following the use of this drug. Corry, Brewer, and Nicol report similar results in the treatment of peritonitis of appendical origin with sulfanilamide. However, it is unfortunate that peritonitis secondary to appendicitis was used as the test case, as in our experience even in cases of generalized peritonitis of appendical origin, 60 per cent of the cases recover with conservative therapy (Sperling and Myrick).

Our interest in the possible use of sulfanilamide intraperitoneally dates back to 1938, when Jensen and his coworkers found that the incidence of infection in compound fractures was less when sulfanilamide was placed in the débrided wound.

At the University of Minnesota Hospitals, sulfanilamide in divided doses of 4 to 6 grams a day is given subcutaneously in most cases of peritonitis irrespective of its origin. On 3 occasions 10 grams of sulfanilamide were poured into the peritoneal cavity at laparotomy when peritonitis was present. While all the patients were critically ill at the time of operation, the fact that 2 of the patients died made us cautious as to the further use of sulfanilamide intraperitoneally in such doses when peritonitis was already present. At present sulfanilamide in doses of 3 to 4 grams is placed in the peritoneal cavity of selected patients when there has been actual or suspected contamination at operation. The powdered sulfanilamide is dusted around the anastomotic sites (3 to 4 grams) and an additional 2 grams are sprinkled also in between the different layers in closing the abdomen. Varco, in this experimental laboratory, has shown a distinctly lowered mortality rate in dogs following complicated gastrointestinal anastomosis when sulfanilamide was used intraperitoneally (unpublished data). Experi-

From the Department of Surgery, University of Minnesota Medical School.

mental work will be presented in this paper which shows that the "preperitonitis" use of sulfanilamide is of some value.

THE USE OF INTRAPERITONEAL VACCINATION AND SUBSTANCES TO PRODUCE INTRAPERITONEAL HYPERLEUCOCYTOSIS

In 1894 Issaef introduced the idea of vaccination to prevent postoperative peritonitis. Pierrelini in 1897 found that a leucocytic exudate could be produced by the intraperitoneal injection of saline solution and other inert substances. Garnier demonstrated that bacteria were rapidly destroyed in the presence of a leucocytic exudate in the peritoneal cavity; his studies showed the importance of phagocytosis in protecting the patient from peritonitis. In 1902, Soleri produced a peritoneal leucocytic exudate in animals and found that animals with such an inflammatory reaction of the peritoneum survived a colon bacillus peritonitis.

In 1922, Johnson first used amniotic fluid to prevent postoperative adhesions and later to protect against peritonitis. He explains the action of amniotic fluid on the peritoneum as one that produces a protective layer of fibrin on the serous surfaces and a moderate local leucocytosis which is followed later by a complete resolution of the fibrinous deposit. He describes the peritoneal reaction as a defense response characterized by hyperemia, marked subserous edema, increase in the peritoneal fluid, and the formation of a pink-tinged fibrinous exudate. There is an increased white cell count that rises rapidly for about 12 hours, at which time the differential count shows a marked preponderance of polymorphonuclear leucocytes. Following this peak, the neutrophils are replaced by histiocytes until the cell count becomes predominately histiocytic. If the exudate is removed from the peritoneal cavity, it forms a fibrinous clot. The peritoneal exudate following intraperitoneal injection of vaccines is profuse and hemorrhagic and does not clot when exposed to air.

Steinberg and Goldblatt began their extensive work on peritonitis in 1926. They showed that intraperitoneal immunization by living and heat-killed colon bacilli produced an immunity in animals to subsequent colon bacillus and fecal peritonitis. They presented convincing evidence that when colon bacilli in saline suspension were injected intraperitoneally they were rapidly absorbed into the blood and lymph, but such animals practically always survived. However, when equal doses of colon bacillus were suspended in 1 per cent gum tragacanth, the animals did not get a bacteriemia but invariably died. One explanation of this was that toxic products of the bacteria were formed in quantity only when they were retained within the peritoneal cavity, and that these toxic products caused the death of the animal.

David and Sparks in 1927 showed that when colon bacilli were injected intraperitoneally they passed readily into the blood and lymph. However, when a plastic peritonitis was first produced by injection of a turpentine emulsion, organisms subsequently injected intraperitoneally could not be recovered from the blood or thoracic lymph.

Herrmann in 1927 showed that in order to produce a peritoneal exudate in rabbits, it was necessary first to build up an immunity before the infecting material was injected. This was successfully carried out by the use of repeated small intraperitoneal doses of a vaccine prepared from the Bacillus coli and Streptococcus viridans. At autopsy the animals showed a true fibrinopurulent peritonitis, but control animals receiving no such immunizing vaccine died with no signs of peritonitis.

In 1931, Morton injected various substances into the peritoneum, such as dextrose broth, heated streptococcic filtrate, various solutions of glucose and saline. Using rabbits he found that he was able to establish a certain degree of protection in most of the animals.

Rice, in 1933, attempted to immunize the peritoneum of dogs by the injection intraperitoneally of a mixture of staphylococcus, streptococcus, and Bacillus coli bacteriophage filtrates. The animals were given the bacterio phage before or at the time of operation which consisted in tying off the cecum in order to produce peritonitis. Bacteriophage failed to immunize the peritoneum in his experiments; moreover the formation of plastic exudate seemed to be inhibited. Jern, Harvey, and

Meleney, working with mice, reported the effect of bacteriophage on peritonitis due to Bacillus coli. They were able to protect the animals against such an infection even when they used doses twenty-five times the size of the lethal doses for controls. The phage was effective when used intraperitoneally before, during, or even several hours after the injection of colon bacilli.

BACTERIOLOGY OF PERITONITIS

Roberts, Johnson, and Bruckner maintain that in the vast majority of human cases the peritoneal cavity is not sterile. They obtained positive cultures in 76 per cent of their cases in which the peritoneum was opened in clean operation. However, these organisms were practically the same as those which they obtained from the deep layers of the skin before the peritoneal cavity was opened, which would seem to indicate their source. The organisms were chiefly diphtheroids or staphylococci which were also found in the laboratory air. Rather surprising was their finding that cultures from frank infections of the peritoneal cavity did not yield a very much higher percentage of positive cultures than cultures from the noninflamed cavity.

The colon bacillus seems to be the commonest organism encountered in peritonitis of intestinal origin. In 1891, Malvoz stated that peritonitis of intestinal origin should not be attributed to any bacteria other than the Bacillus coli. In 1938 Altemeier reviewed the literature of the bacteriology in perforated appendicitis. Most of the authors quoted by Altemeier believed the Bacillus coli to be the commonest organism encountered, although he found the bacterial flora in some cases to be very complicated and bizarre. Owen studied cultures or peritoneal fluids of animals injected intraperitoneally with suspensions of total cecal contents of normal animals, usually the guinea pig. Such cultures revealed members of the coliform group of bacteria in 51 per cent of the cases. Cultures from animals dying of the infection showed the organisms in 84 per cent of the cases while in animals that survived 16 per cent of cases showed these organisms. Streptococci were seldom found and pathogenicity tests gave comparatively low death rates. Mixed cultures of streptococci and coliform organisms killed some animals but the streptococci could seldom be found in the peritoneal fluids of animals dead of these injections.

CELLULAR EXUDATE IN PERITONITIS

It has been established from animal experiments and clinically in patients that the introduction of foreign substances into the peritoneal cavity will excite the production of a defensive cellular exudate. The contents and volume of this exudate will be determined to a large extent by the character and amount of the substances involved. This reaction is characterized locally by hyperemia, increase in the peritoneal fluid, increase in the histiocytic and leucocytic counts and phagocytosis.

There is no uniformity of opinion as to the relative protective functions of the polymorphonuclear leucocytes and the histiocytes. Steinberg regards the polymorphonuclear as the important phagocytic cell and feels that the histiocyte is a scavenger cell which appears late in peritonitis when it engulfs the degenerated polymorphonuclear leucocytes. Coller and Brinkman also believe that the polymorphonuclear leucocyte is the important cell in phagocytosis. Johnson among others believes that the histiocyte is a superphagocyte and comes into the picture late in response to dead tissue. However, Herrmann expressed his belief that the histiocyte is probably the most important cell concerned with phagocytosis.

Garnier, Wilkie, and Coller and Brinkman found examination of the peritoneal exudate to be of value in determining the progress of acute peritonitis. It should be emphasized, however, that local immunity cannot be measured in terms of one total or differential leucocytic count alone. Other factors, chiefly humoral, play an important part (Johnson, McCollum).

In 1938, Rixford studied at operation the peritoneal fluid of patients who had previously received intraperitoneal vaccine and compared these findings with a control group of patients which had received no vaccine. Specimens were taken with a glass pipette just after the peritoneal cavity was opened. In

unvaccinated cases, the total white cell count averaged from 1900 to 2600 per cubic millimeters of fluid. There were practically no neutrophils, very few eosinophils and basophils, but many lymphocytes and histiocytes —45 per cent. In patients who had been vaccinated 24 to 144 hours prior to operation, specimens of peritoneal fluids were also examined. There was considerable variation in the findings, but it was apparent that there was an early increase in polymorphonuclear cells and a delayed but marked increase in histiocytes.

Seeley, Higgins, and Mann observed the cytological response of the peritoneal fluid of rats to injections of amniotic fluid concentrate, Bargen's vaccine—prepared from colon bacilli and nonhemolytic streptococci—and sodium ricinoleate. They found that with all materials there was an early and rapid rise of polymorphonuclear leucocytes, reaching a maximum in 3 to 6 hours. Histiocytes appeared much later but were the preponderant cells after 6 or 7 days. The response of both cells was greater in those animals receiving sodium ricinoleate.

In 1937, Corwin reported that in the rabbit, the cellular responses to Bargen's vaccine and sodium ricinoleate were nearly identical qualitatively. However, with Bargen's vaccine the cell count of the peritoneal fluid was greatest at 12 hours, with 1 per cent sodium ricinoleate at 24 hours and with 2 per cent sodium ricinoleate at 48 hours. The differential count showed the polymorphonuclear to appear early, being in greatest abundance in 6 to 12 hours, while the histiocytes were maximal in 1 to 3 days. Whereas the cell count per cubic millimeter after injection of sodium ricinoleate was only 40,000, the total amount of fluid was so much greater that a greater total number of cells was evoked by the ricinoleate than by Bargen's vaccine.

Coller and Rife, in their review of the cellular aspect of immunization, state that the variation in opinion regarding the relative phagocytic properties of the neutrophil and histiocyte is due in part to the use of different species of animals by different workers. Also the type of material used, the dosage employed, the time intervals for examination of the fluids are not constant in the different studies.

CLINICAL RESULTS FOLLOWING THE USE OF INTRAPERITONEAL VACCINES AND OTHER SUBSTANCES

Steinberg and Goldblatt developed a protective emulsion consisting of Escherichia coli in tragacanth, which they call coli-bactragen.[1] This substance will protect the experimental animal from certain types of subsequently-induced peritonitis. Steinberg has demonstrated protection against living colon bacilli, Streptococcus fecalis, Bacillus pyocyaneus, and Clostridium welchii, in both pure and mixed cultures.

In 1934 Goldblatt reported a collected series of 400 patients receiving coli-bactragen. Eight postoperative deaths were recorded but only 3 of these could be attributed to peritonitis. The operations were performed by various surgeons and consisted chiefly of resections of the large bowel. The first preparation of coli-bactragen was injected intraperitoneally about 24 hours before operation and was frequently accompanied by a rather severe general reaction. The more recent preparations of coli-bactragen produce a less severe general reaction and achieve maximum protection within a few hours.

In 1934, Potter and Coller reported a series of 79 patients, most of whom had major operations performed upon the colon, who were given coli-bactragen before operation. There were 11 deaths, in only one of which was the lethal outcome attributed to peritonitis. Although the series was small and not controlled, they were of the opinion that vaccine was probably not indicated except in cases of gross fecal contamination. In 1936, Coller and Ransom reported the use of coli-bactragen in 79 cases which had a combined abdominoperitoneal resection for carcinoma of the rectum and rectosigmoid. There were 12 deaths, but in none was death believed to be due to peritonitis. In the same year Steinberg reported 391 cases in which coli-bactragen was used before operation or at the time of operation with none developing postoperative peritonitis.

[1]Coli-bactragen (Steinberg) consists of 50 billion bacteria per 30 cubic centimeters with 1 per cent of 1:10,000 merthiolate suspended in 1.5 per cent gum tragacanth.

In 1928, Bargen developed his vaccine prepared from streptococci and colon bacilli. It was given intraperitoneally 3 days before intestinal operations. In 1935 Dixon and Bargen reported 1,500 cases in which the vaccine had been used with a reduction of 66 per cent in the mortality rate from postoperative peritonitis. The vaccine was attended with degrees of general systemic reaction. In 1930 Rankin, in a review of 527 surgical lesions of the large intestine and rectum in which peritoneal vaccination was used before operation, reported a mortality rate of 12.3 per cent by patient and 8.6 per cent by operation. In 1933 he reported a new series in which the vaccine was not used. In 200 consecutive operations upon the colon and rectum, he reported a mortality of 5.5 per cent by operation and 8.4 per cent by patient. He attributed the decline in mortality to better preoperative preparation rather than to vaccination.

Johnson, Warren, Trusler, Young and Marks, Klimpton, and others have reported their results with the use of amniotic fluid concentrates. Young and Mark reported upon the use of amniotic fluid concentrates in 49 cases which involved chiefly operations on the colon. There were 3 deaths, but in only 1 instance could death be attributed to postoperative peritonitis. In a series of 46 similar cases in which amniotic fluid was not used before operation, there were 8 deaths, 17.3 per cent. In the cases of colonic reaction the mortality was 38 per cent in the control series. Gepfert believes the postoperative convalescence is smoother in patients receiving amniotic fluid.

SERUM

Many clinical studies have appeared in the literature concerning the treatment of peritonitis with various sera. Very little experimental work has been done, however. It is impossible to tabulate or evaluate different series, as the type of serum and method of administration vary widely.

The following antigens have been employed: (1) Bacillus coli filtrate; (2) toxins of Clostridium welchii or of combined anaerobes; (3) a combination of colon and gas bacillus; (4) enterococci, usually added to colon bacilli and anaerobes; (5) bacterial bodies as well as colon and gas bacilli; (6) a number of other organisms such as the Bacillus fusiformis, Bacillus fundiliformis, staphylococcus, and intestinal streptococci which have produced a serum to which is added polyvalent antigas-gangrene serum and anticolic serum (Harvey and Meleney).

It should be mentioned that not all the anaerobes found in the exudate in peritonitis are virulent. Also, it is not known that a serum produced against one strain of Bacillus coli will be effective against other strains of the same organism. For these reasons, it is doubtful that potent sera can be produced commercially according to our present knowledge.

The first use of Bacillus coli serum has been attributed to Guthrie (1915); he used serum together with coli vaccine only in patients who underwent operation and in whom the diagnosis was doubtful. Most of the reports of the clinical use of serum have been in the foreign literature (Vincent, Weinberg, Riemann, Kunz, Pellegrini). In this country Priestley and McCormack reported favorable results in a small group of cases.

One of the best reports is that of Riemann. He reported 368 cases of peritonitis in which either coli serum or a combined "peritonitis serum" was used during the period from 1931 to 1933. He saw no difference in results from the two types of sera. Of 368 cases of peritonitis, 244 followed appendicitis with a 4.5 per cent mortality and 124 followed other lesions with a 20.9 per cent mortality. In previous 3 year periods without the use of serum, the mortality has been from 21.7 per cent to 22.5 per cent for peritonitis following appendicitis and from 37.7 to 38.4 per cent for peritonitis following other causes. Riemann never used over 100 cubic centimeters of serum in treating a case.

On the other hand, Kapel, of Copenhagen, and Urech, of Switzerland, after they had made a fairly extensive clinical trial, found no benefit from serum in cases of peritonitis. Santi had the opportunity to try serum in 14 cases in which for one reason or another an operation was not attempted. Nine of 14 patients died.

Perrando, Chiari and Kunz, Trusler and Moss have reported experimental evidence showing that antiserum gives some protection against peritonitis. However, the series of animals was small and the specificity of the antisera not proved.

DEEP X-RAY THERAPY IN THE TREATMENT OF PERITONITIS

For many years, deep x-ray therapy has been used in the treatment of acute and chronic infections. The use of deep x-ray irradiation in the treatment of gas bacillus infections has quite a vogue at the present time. There are occasional case reports concerning the treatment of pneumonia, peritonitis, cellulitis, etc., by irradiation, but most of these are poorly controlled and irradiation was not the only form of therapy used in many instances.

Pratt reported that the preoperative irradiation of the abdomen and pelvis of patients with carcinoma of the colon reduces the incidence of peritonitis. Kelly and Dowell advise irradiation of the abdomen in some patients with peritonitis due to rupture of the appendix. Altemeier and Jones believe roentgen therapy to be of value in immunizing animals against peritonitis. The maximum degree of immunity in animals occurred from 4 to 6 weeks after irradiation. As Blalock remarks, it is too early to appraise the value of this type of therapy at the present time.

Desjardins, from clinical observations and an extensive review of the experimental and clinical reports on the treatment of inflammations with x-rays, suggests that the leucocytes undergo lysis when irradiated, and in this lytic process antibodies are freed in the infected area. Kelly agrees with this idea. Experiments concerning the use of deep x-ray therapy in the treatment of peritonitis in rabbits will be discussed later.

EXPERIMENTAL DATA—GENERAL CONSIDERATIONS

The ideal activator of peritoneal immunity is a substance which clinical analysis and extensive clinical and laboratory trial has proved to be innocuous; one which may be used before or at operation without discomfort or clinical upset; one which has an immunizing interval sufficiently brief to be adaptable to operative introduction; one which will induce a peritoneal reaction similar to that laid down by the normal peritoneum in the presence of infection. In addition, the agent should be stable and free from remote untoward reaction (Johnson and coworkers).

A number of substances has been used to try to prevent peritonitis. As early as 1885, an attempt was made to immunize the peritoneum by colon bacillus vaccine (Mikulicz) but because of the severe reactions that occurred, it was largely given up. Later peritoneal immunization was reported following the use of nonspecific substances, as peptone broth, saline, sterile water, serum, egg albumin, dextrose, and certain drugs and chemicals. Of late years, the following substances have enjoyed a certain popularity: antiperitonitis vaccine (Bargen, Rankin, Dixon), coli-bactragen (Steinberg), coli antiserum (Trusler and Moss), sodium ricinoleate (Seeley and Larson), and sulfanilamide.

It is difficult to evaluate the efficacy of these various agents in preventing peritonitis in clinical cases because factors, as the type of case, the drug and dosages used, time interval, etc., vary so widely. Moreover, it is not justifiable to use critically sick people as controls.

In all immunological studies it is important to realize that all immunity is relative in both a qualitative and quantitative sense; that is, if the dose or virulence of the organism is greater than the protective titre of the substance to be tested, the animal will die. Therefore, experimentally, unless quantitative as well as qualitative factors are controlled, the results are relatively meaningless.

Method. The peritoneal exudate from patients dying of peritonitis was chiefly used. This material was collected and the organisms examined as to number and identity. Several loopfuls of the material were inoculated into liver peptone broth. After 24 hours of incubation, a smear was made and stained by Gram's method. A loopful of the liver peptone culture was streaked upon blood agar and eosin-methylene blue plates for identification of organisms. Another loopful was inoculated into a tube of sterile milk and incubated at

37 degrees C. for 6 to 24 hours for determination of anaerobes.

To count the number of bacteria, the culture was drawn up to a mark on a capillary pipette; blood was drawn up to the same mark and the contents of the pipette blown out on a slide and mixed. A smear was made and stained by Wright's method. The number of bacteria and red cells in 100 fields were counted and averaged. The number of bacteria were calculated by proportion.

$$\frac{\text{Average number of bacteria per field} \times \text{erythrocyte count per c. mm.}}{\text{Average number of red blood cells per field}} = \text{No. of bacteria per c.cm.}$$

Full grown, stock rabbits were used as the experimental animal. In each case the culture used was 24 hours old. In a few experiments the rabbit was anesthetized with drop ether, the abdomen was opened under sterile precautions, and the culture was placed in the peritoneal cavity followed by the drug to be tested. In most of the experiments, however, the culture was injected into the peritoneal cavity of unanesthetized rabbits followed after a few minutes' interval by an injection of the drug through the same needle. Control experiments were carried out. The animals were observed up to a period of 2 weeks following injection.

The survival rate was studied as well as the incidence of peritonitis, as the animals that survived the 2 week period were not sacrificed to see if they had peritonitis. Animals that died within 24 hours after injection of the culture showed little evidence of peritonitis and probably died of a bacteriemia.

The following substances were tested: sodium ricinoleate 1 per cent as prepared by Dr. W. Larson, department of bacteriology, University of Minnesota Medical School; ether U.S.P.; tincture of merthiolate; mercurochrome, 2 per cent (aqua); S. T. 37; hydrochloric acid, 0.5 per cent; hydrochloric acid, 1 per cent; cow serum; coli-bactragen (Steinberg); immune rabbit serum from 2 sources; amniotic fluid concentrate (Eli Lilly); sulfanilamide. Bovine serum was tried because of its well known resistance to peritonitis. Immune rabbit serum was obtained as follows: A cardiac puncture was performed on rabbits that survived 10 to 14 days following the injection of a peritoneal exudate. After the clotted blood was centrifuged, the agglutination titer of the pooled serum against Escherichia coli was determined. This serum was injected intravenously into other rabbits to note its protective power against peritonitis. This is, in essence, an immunotransfusion. "Hyperimmune" serum was made from blood of rabbits that survived 5 injections 2.5 cubic centimeters each, of a purulent peritoneal exudate given over a period of 2 weeks. This exudate contained Escherichia coli and Streptococcus viridans, 250,000,000 organisms per cubic centimeter.

RESULTS

Experiment 1. Culture: 2 cubic centimeters of brain broth of a peritoneal exudate containing Streptococcus viridans; Staphylococcus aureus, aerogenes; unidentified gram negative and positive rods and cocci; and Escherichia coli.

No quantitative study of the organisms was made.

The rabbits were anesthetized with ether, and the abdomen was opened under sterile precautions. Two cubic centimeters of the culture was added and then 5 cubic centimeters of the drug to be tested.

EXPERIMENT I

Drug	No. of animals	Dead			Living		
		No.	Duration days	Peritonitis	No.	Duration days	Peritonitis
Controls	8	6	3	6	2	14	2
Sodium ricinoleate, 1%	8	1	2	1	7	14	1
Ether	8	2	3	2	6	14	1
Tincture merthiolate	8	2	1.3	2	6	14	4
S. T. 37	8	3	1.4	3	5	14	3
Mercurochrome, 2%	8	4	1.3	4	4	10	4
Hydrochloric acid 0.5%	8	2	1.4	2	6	10	6*
Hydrochloric acid 1%	8	2	1.2	3	6	10	4*

*Bowel locally was burned by acid with scattered splattered areas.

In this experiment, sodium ricinoleate 1 per cent, ether, and tincture of merthiolate were the most effective drugs in preventing peritonitis.

Experiment 2. Culture: 2 cubic centimeters of veal broth containing Streptococcus viridans, Escherichia coli, and Clostridium welchii, a total of 500,000,000 organisms per cubic centimeter.

The rabbits were injected intraperitoneally with 2 cubic centimeters of culture followed by 5 cubic centimeters of drug, through the same needle.

EXPERIMENT 2

Drug	No. of animals	Dead			Living		
		No.	Duration hours	Peritonitis	No.	Duration days	Peritonitis
Controls	5	5	24	2			
Sodium ricinoleate, 1%	5	4	24	1	1	10	
Ether	5	4	24	2	1	10	
Tincture of merthiolate	5	5	24	2			

This culture was too virulent. The animals probably died of bacteriemia.

Experiment 3. Culture: 2 cubic centimeters of veal broth containing Escherichia coli and Streptococcus viridans, a total of 250,000,000 organisms per cubic centimeter.

The culture was injected into rabbits intraperitoneally, followed by injection of 5 cubic centimeters of the drug through the same needle.

EXPERIMENT 3

Drug	No. of animals	Dead			Living		
		No.	Duration hours	Peritonitis	No.	Duration days	Peritonitis
Controls	5	2	24		3	3	2
Sodium ricinoleate, 1%	5	0	24		5	3	1
Ether	5	4	24	3	1	3	
Tincture merthiolate	5	1	24		4	3	2

With a less virulent culture the longest survival rate was in animals injected with sodium ricinoleate 1 per cent.

Experiment 4A. Culture: 5 cubic centimeters of cecal content of rabbit was added to 10 cubic centimeters of tap water.

Under ether anesthesia to sterile precautions, the abdomen of the rabbit was opened and 5 cubic centimeters of suspension was added and then 5 cubic centimeters of the drug to be tested.

EXPERIMENT 4A

Drug	No. of animals	Dead			Living		
		No.	Duration days	Peritonitis	No.	Duration days	Peritonitis
Controls	5	3	72	2	2	10	2
Sodium ricinoleate, 1%	5	1	72	1	4	10	0
Ether	5	3	1	1	2	10	0
Tincture merthiolate	5	2	2	2	3	10	1

EXPERIMENT 4B

Drug	No. of animals	Dead			Living		
		No.	Duration days	Peritonitis	No.	Duration days	Peritonitis
Control	5	4	3	4	1	7	0
Sodium ricinoleate, 1%	5	0	0	0	5	7	1
Ether	5	3	1	1	2	7	0
Tincture merthiolate	5	2	1	1	3	7	1

Experiment 4B. Culture: Same as in experiment 4A.

The rabbits were injected with 5 cubic centimeters of the culture intraperitoneally, followed by 5 cubic centimeters of the drug to be tested, through same needle.

In experiments 4A and 4B, sodium ricinoleate, 1 per cent, also proved to be the most effective drug in the prevention of peritonitis in rabbits.

Experiment 5A. Culture: Stool of patient with chronic ulcerative colitis, containing Streptococcus viridans and Escherichia coli, unidentified gram positive and negative rods and cocci, 2,000,000,000 organisms per cubic centimeter.

The rabbits were injected with 2.5 cubic centimeters of fecal material intraperitoneally, which injection was followed by 3 cubic centimeters of the agent to be tested.

EXPERIMENT 5A

Drug	No. of animals	Living	Dead
Controls	5	2	3
Bovine serum	4	4	0
Coli-bactragen	5	3	2
Amniotic fluid (Eli Lilly)	6	2	4

Experiment 5B. Culture: Same as in experiment 5A.

The same technique was used as in experiment 5A. except that 5 cubic centimeters of the drug to be tested was used.

EXPERIMENT 5B

Drug	No. of animals	Living	Dead
Controls	8	0	8
Bovine serum	8	1	7
Coli-bactragen	8	3	5
Amniotic fluid (Eli Lilly)	6	3	3

SUMMARY OF EXPERIMENTS 5A AND 5B

Drug	No. of animals	Living	Dead
Controls	13	2	11
Bovine serum	12	5	7
Coli-bactragen	13	6	7
Amniotic fluid (Eli Lilly)	12	5	7

Coli-bactragen and amniotin were effective in only about half of the cases and were only slightly more effective than bovine serum.

Experiment 6. Peritoneal fluid of a patient dying from peritonitis, containing Streptococcus viridans and aerogenes, and Escherichia coli, 2,900,000,000 organisms per cubic centimeter. The specific gravity of the peritoneal exudate was 1.042.

Two and one-half cubic centimeters of the peritoneal exudate was injected intraperitoneally into rabbit followed by the drug to be tested.

EXPERIMENT 6

Drug	No. of animals	Living	Dead
Controls	8	0	8
5 c.cm. sodium ricinoleate, 1%	8	3	5
10 c.cm. sodium ricinoleate, 1%	8	5	3
10 c.cm. cow serum	8	4	4
10 c.cm. coli-bactragen	8	3	5

Sodium ricinoleate, 1 per cent, was more effective in 10 cubic centimeters than in 5 cubic centimeters dose and was more effective than bovine or coli-bactragen.

Experiment 7. Culture was same as that used in experiment 6, except it was incubated 48 hours at 37 degrees. It contained Streptococcus viridans and Escherichia coli, 2 billion organisms per cubic centimeter.

The method was the same as that used in experiment 6.

EXPERIMENT 7

Drug	No. of animals	Living	Dead
Controls	5	4	1
5 c.cm. immune serum	8	5	3
10 c.cm. sodium ricinoleate, 1%	7	4	3
10 c.cm. coli-bactragen	8	3	5

The animals treated with 5 cubic centimeters of immune serum injected intravenously seemed to be protected as well if not better than those that received sodium ricinoleate, 1 per cent, or coli-bactragen.

Experiment 8. Culture: Peritoneal exudate from a case of fatal peritonitis. It contained Escherichia coli, Staphylococcus aureus, Streptococcus hemolyticus, 2,400,000,000 organisms per cubic centimeter.

Five cubic centimeters of peritoneal exudate was injected intraperitoneally into rabbits with 5 cubic centimeters of immune rabbit serum intravenously at the same time. In other rabbits immune serum had been injected subcutaneously 7 days before the intraperitoneal injection of 5 cubic centimeters of peritoneal exudate.

EXPERIMENT 8

Drug	No. of animals	Living	Dead
Controls	6	2	4
5 c.cm. immune serum intravenously	8	4	4
5 c.cm. immune serum (injected subcutaneously 7 days before experiment)	8	2	6

"Immune" serum seems to be of value in protecting rabbits against peritonitis; it must be given intravenously. The subcutaneous injection of the serum 7 days before the experiment was of little value.

Experiment 9. Culture: Pus from infected wound 3 weeks after appendectomy; contained Escherichia coli, nonhemolytic streptococci, unidentified gram positive and negative rods and cocci, 2 billion organisms per cubic centimeter.

Blood from this patient was taken, allowed to clot, centrifuged. Agglutination titer 1:1280 for Escherichia coli. This immune serum was injected intravenously into rabbits. Also these animals were given intraperitoneally 2.5 cubic centimeters of the above culture which was incubated in veal broth, each cubic centimeter containing 250,000,000 organisms.

EXPERIMENT 9

Drug	No. of animals	Living	Dead
Controls	6	2	4
5 c.cm. human "immune" serum	7	5	2

The human "immune" serum in this case, when injected intravenously into rabbits receiving the above culture intraperitoneally gave definite protection against peritonitis. While there may have been antibodies against other organisms in the serum, only the ag-

glutinins for Escherichia coli were determined, as it was the predominant organism.

Experiment 10. The purpose of this experiment was to note the effect of serum which had a low agglutination titer in protecting against peritonitis.

Culture: Exudate from a fatal case of peritonitis containing Escherichia coli, Streptococcus viridans, unidentified gram positive and negative rods and cocci: contained 29,000,000,000 organisms per cubic centimeter.

Blood was taken from patient with carcinoma of the cecum with fistulous formation. Culture from the fistulous tract was sterile. Agglutination titer blood was negative for Escherichia coli.

EXPERIMENT 10

Drug	No. of animals	Living	Dead
Controls	5	2	3
5 c.cm. human "immune" serum	4	1	3

This serum with no agglutinins for Escherichia coli gave no protection against peritonitis.

Experiment 11. Culture: Peritoneal exudate containing Escherichia coli, Streptococcus viridans, 2,900,000,000 organisms per cubic centimeter.

Rabbits were injected with 2.5 cubic centimeters exudate intraperitoneally and 5 cubic centimeters of hyperimmune rabbit serum intravenously. Agglutination titer 1:6400 for Escherichia coli.

EXPERIMENT 11

Drug	No. of animals	Living	Dead
Controls	8	3	5
5 c.cm. hyperimmune serum (1:6400)	8	6	2

Hyperimmune rabbit serum (agglutination titer 1:5120 against Escherichia coli) gave definite protection against peritonitis.

Experiment 12. Culture: the same was used as in experiment 11.

The method used was the same as that in experiment 11, except that hyperimmune rabbit serum (agglutination titer 1:1280) was used.

EXPERIMENT 12

Drug	No. of animals	Living	Dead
Control	8	2	6
5 c.cm. hyperimmune rabbit serum (agglutination titer 1:1280 Escherichia coli)	8	7	1

Hyperimmune rabbit serum with an agglutination titer of 1:1280 against Escherichia coli gave definite protection against peritonitis.

Experiment 13. Culture: Intestinal content of dog with low ileal obstruction. Contained Staphylococcus aureus 2,400,000,000 per cubic centimeter, Streptococcus hemolyticus 250,000,000 per cubic centimeter, Clostridium welchii, and Escherichia coli. each 500,000,000 per cubic centimeter.

Under ether anesthesia the abdomen of the rabbit was opened and 1 to 5 cubic centimeters of obstructed ileal content was poured into it, followed by 5 cubic centimeters of sodium ricinoleate 1 per cent or 1 gram sulfanilamide. Eight animals were used in each series.

EXPERIMENT 13

Culture	Controls		Sodium ricinoleate, %		Sulfanilamide	
	Living	Dead	Living	Dead	Living	Dead
5 c.cm. obstructed ileum content	0	8	3	5	2	6
2 c.cm. obstructed ileum content	0	8	3	5	0	8
1 c.cm. obstructed ileum content	2	6	2	5	4	4
1 c.cm. obstructed ileum content	1	7	4	3	2	5

With this culture, sodium ricinoleate, 1 per cent, was more effective than sulfanilamide in protecting the rabbits, but sodium ricinoleate, 1 per cent was effective in only 40 per cent of the cases.

Experiment 14. Culture: Peritoneal exudate from a fatal case of peritonitis contained Escherichia coli at least 2,000,000,000 organisms per cubic centimeter, Streptococcus hemolyticus 1,000,000,000 organisms, Staphylococcus albus, gram negative and positive rods and cocci, aerogenes, and unidentified gas formers.

Three cubic centimeters of exudate was injected into the peritoneal cavity of rabbits followed by 3 cubic centimeters of the substance to be tested. When sulfanilamide was tested, 10 grams of the powder was suspended in 30 cubic centimeters of tap water, and 3 cubic centimeters of the thoroughly stirred mixture injected through a No. 15 needle into the peritoneal cavity of the rabbit.

EXPERIMENT 14

Drug	No. of animals	Living	Dead
Controls	10	2	8
Sulfanilamide (1 gm.)	10	5	5
Coli-bactragen 3 c.cm.	10	4	6
Sodium ricinoleate 1%, 3 c.cm.	10	4	6

In this experiment, sulfanilamide proved to be the most effective agent. Coli-bactragen and sodium ricinoleate, 1 per cent, were equally effective in preventing peritonitis.

Experiment 15. Culture: Same as in experiment 14.

(a) Under ether anesthesia, the abdomen of the rabbit was opened and 5 cubic centimeters of the culture added followed by 1 gram of powdered sulfanilamide in the peritoneal cavity. (b) Under ether anesthesia, 1 gram of sulfanilamide was placed under the skin on the back. Five cubic centimeters of above culture was injected peritoneally. (c) Rabbits were given 20 cubic centimeters of 0.8 per cent sulfanilamide solution (80 mgm.) subcutaneously every day for 5 days and then 5 cubic centimeters of above culture was injected intraperitoneally.

EXPERIMENT 15

Method	No. of animals	Living	Dead
5 c.cm. culture plus 1 gm. sulfanilamide intraperitoneally	8	7	1
5 c.cm. culture intraperitoneally plus 1 gm. sulfanilamide subcutaneously	4	0	4
5 c.cm. culture intraperitoneally plus 20 c.cm. 0.8 per cent sulfanilamide subcutaneously daily for 5 days (total 0.8 gms.)	8	5	3
Controls	6	1	5

Sulfanilamide placed intraperitoneally at the same time as the culture gave excellent protection against death from peritonitis. Placing the sulfanilamide subcutaneously at the same time as the culture was injected intraperitoneally gave no protection. However, giving the sulfanilamide subcutaneously daily for 5 days before injecting the culture intraperitoneally gave some protection but not as much as that following placing the sulfanilamide in the abdomen.

Experiment 16. Culture: Peritoneal exudate of patient dying from peritonitis, containing Streptococcus viridans and aerogenes, Escherichia coli and Streptococcus hemolyticus, 2,500,000,000 per cubic centimeter.

Five cubic centimeters was injected intraperitoneally into rabbits. Within 24 hours 5 rabbits so treated were anesthetized and the abdomen was opened. Peritonitis was present in all. One gram of sulfanilamide was sprinkled into the peritoneal cavity. None of the animals survived more than 48 hours.

While the ether anesthesia may have contributed to the deaths of the animals, sulfanilamide intraperitoneally was of little or no value in treating the peritonitis once it was well established. This experiment has also been tried in 8 guinea pigs with peritonitis. No protection from the intraperitoneal use of sulfanilamide has resulted once the peritonitis is well established.

Experiment 17. (a) Effect of irradiation on the cell count of peritoneal fluid.

Three rabbits were treated by means of x-ray therapy to the abdomen. The method was as follows: 250 roentgens were given to the anterior abdominal wall, 220 kilovolts, 60 centimeter distance with 1 aluminum filter.

Three days later, the abdomen of three of the rabbits was opened and the cellular content of the peritoneal fluid was studied. There were only an occasional histiocyte and leucocyte found, and total counts were no greater than those of 3 control rabbits (500 to 1800 cells per c.cm.). The animals were not studied for longer periods because the efficacy of irradiation therapy should be apparent within the first few days after the peritonitis has developed, if the protection is on the basis of hyperleucocytosis.

(b) Because deep x-ray therapy may give a protection other than cellular to the peritoneum against invading organisms, the following experiments were carried out. (1) 5 c.cm. of peritoneal exudate was injected into the abdomens of unanesthetized rabbits. The rabbits were then given deep x-ray therapy to the abdomen by the method described. (2) Culture contained Escherichia coli 2,500,000,000 per cubic centimeter. Streptococcus hemolyticus 500,000,000 per cubic centimeter, aerogenes, Staphylococcus albus.

EXPERIMENT 17

	No. of animals	Living	Dead
Controls	6	2	4
Deep x-ray	6	1	5

Dr. Carl Lind, Walter Reed Hospital, Washington, and Dr. Clarence Truog, Miami, Florida, who were then in the department of radiotherapy, aided in this experiment.

In this small series, irradiation was of little value in protecting the animals against peritonitis. In another series, 4 rabbits that were ill with peritonitis, all died in spite of irradiation therapy.

Experiment 18. Culture: Peritoneal exudate from a fatal case of peritonitis, containing Staphylococcus aureus, Streptococcus viridans, Escherichia coli, and unidentified gram positive and negative rods and cocci, 2,500,000,000 organisms per cubic centimeter.

Five cubic centimeters of culture was placed in the peritoneal cavity of anesthetized rabbits and 1 gram of sulfathiazole powdered in.

EXPERIMENT 18

Drug	No. of animals	Living	Dead
Control	8	2	6
Sulfanilamide	10	4	6
Sulfathiazole	10	5	5

Sulfathiazole and sulfanilamide were about equally effective in protecting the animals in this series.

SUMMARY AND ANALYSIS OF EXPERIMENTAL DATA

It is apparent that there is no cure-all for peritonitis. At best, only about half the animals could be protected regardless of the agent tested. Of the substances used in this study, amfetin and coli-bactragen were no more effective than sodium ricinoleate, 1 per cent, as far as the survival rates were concerned. The results obtained with the sulfonamides were impressive, but it may be questioned if the results obtained were significantly better than those obtained with sodium ricinoleate, coli-bactragen, etc.

Sulfanilamide would seem to be most effective in the preperitonitis stage. Once peritonitis has developed, its efficacy is much reduced. Moreover, the direct application of sulfanilamide would seem to be more effective than the subcutaneous administration of the drug or the placing of an equivalent amount of the powder under the skin.

At this clinic sulfanilamide in doses of 3 grams has been placed in the peritoneal cavity at operation when there was suspected or actual contamination. If frank purulent peritonitis is present, sulfanilamide is not only of little value because it will be inactivated by the protein of the exudate, but it is contraindicated as it may aggravate a hepatitis already caused by the peritoneal infection. Clinically sulfathiazole may prove to be more effective than sulfanilamide in the treatment of peritonitis, as the former is less toxic to the liver.

In "clean" cases, there is no indication for the use or any of these agents. In clean incision of the skin in dogs, sulfanilamide affords no higher incidence of healing by primary intention (Jensen and Rea, unpublished data).

In "dirty" or grossly infected wounds, sulfanilamide is valueless, unless a thorough débridement or cleansing of the wound is performed first. Jensen, Nelson, and Johnsrud found that sulfanilamide was most effective in compound fractures before there was any sign of gross infection. Moreover, in infected compound fractures, if sulfanilamide were placed in the wound before débridement or a thorough cleansing, no benefit was obtained. Similarly, in peritonitis, sulfanilamide is most effective in the preperitonitis stage. When peritonitis is present, its value is questionable.

In the few experiments performed, and in the dosage used, radiation therapy gave little or no protection against peritonitis in rabbits.

The use of hyperimmune serum would seem to be of value in preventing peritonitis in rabbits. A feasible plan for its use in human cases has not been worked out as yet.

CONCLUSIONS

1. In reviewing the literature, many agents have been used in treating peritonitis.

2. Clinically it is difficult to judge the value of certain substances in preventing peritonitis, as factors such as the amount and type of contamination at operation, organisms present, type of operative procedure performed, the experience of the surgeon, the condition of the patient, etc., have to be considered.

3. In experimental peritonitis, unless qualitative and quantitative factors, such as the number and type of organisms present, are controlled, the results are meaningless.

4. In these experiments, the effect of certain substances in preventing peritonitis in rabbits was studied, controlling the number and type of organisms injected to cause the peritonitis. Unfortunately the same culture could not be used in all the experiments. Of the substances tested, however, none was effective in more than 50 per cent of cases. Sodium ricinoleate, coli-bactragen and the sulfonamides were most effective of the substances tested. It may be questioned if sulfanilamide is superior to the other substances tested in preventing peritonitis.

5. Regarding the use of sulfanilamide in the peritoneal cavity: (a) it is not indicated in clean cases; (b) it is most effective in the pre-peritonitis stage; (c) it is more effective if placed in the peritoneal cavity than if placed under the skin; (d) it is of relatively little value in cases of frank purulent peritonitis.

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DERMOVASCULAR EFFECTS OF ESTROGEN IN WOMEN WITH MENOPAUSAL FLUSHES

SAMUEL R. M. REYNOLDS, Ph.D., SANFORD KAMINESTER, M.D., F.A.C.S., FRANCES I. FOSTER, B.S., and STEWART SCHLOSS, M.D., Brooklyn, New York

IT has been observed recently that estrogen has a vasodilating effect upon the smallest blood vessels of the skin,—a dermovascular action. This has been seen directly in the ear of the rabbit (3), and attested indirectly in this species by noting a 13 per cent reduction in transmitted light following injection of the hormone (2). In the human male, a similar effect has been noted; estrogen causes a 4.6 per cent increase, on the average, in the size of the finger (4). This is confined to the smallest blood vessels beyond the arterioles, as shown by reasons which will be enumerated.

The present experiments on women in the menopause were carried out as a counterpart to the earlier ones in the male. Particular point is given these newer observations, however, inasmuch as there is as yet no precise information concerning the nature of the mechanism by which estrogen contributes to the relief of vasomotor flushes of the climacteric. The hypothesis that it is concerned in some way with depression of an overactive pituitary gland (1) leaves unanswered the question of how this, in turn, affects the vasomotor system, on one hand, and there is evidence, on the other, to show that an overactive anterior hypophysis is not necessarily manifested by disturbances of the vasomotor system (3). It appeared likely, therefore, that some clue concerning the therapeutic efficacy of estrogen in the menopause might come from a study of the peripheral vascular action of estrogen in carefully selected patients. The following account records the first of our observations along these lines.

From the Department of Physiology, Long Island College of Medicine, and the Gynecologic Service of the Long Island College of Medicine, Greenpoint Hospital.

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PATIENTS AND PROCEDURES

Twenty-four patients were directed to us from a large number attending the Outpatient Clinic of the Greenpoint Hospital. The only complaint in these cases was that of intense and frequent flushes from which the patients sought relief. After careful examination, it was established that the individuals were free of other important medical complications. Even so, it was found subsequently that 6 were unsuited to or unco-operative for the purposes of this work, and so were not employed. Of the remainder, 13 were in artificial menopause, 4 were in natural menopause, and 1 was still menstruating.

As a result of intensive observation, it was learned early in the course of study that these patients could be divided into 2 groups. One—3 in surgical menopause, 4 in natural menopause—was promptly relieved of the vascular disturbances by means of estrogenic hormone; there appeared to be no other important contributing factor to the etiology of the menopause syndrome than that of primary ovarian deficiency. The other group—8 in surgical menopause, 2 in irradiation menopause, and 1 still menstruating with premenstrual tension and menometrorrhagia—obtained little relief with estrogen or sedatives, but they responded well, for the most part, to correction of a psychogenic factor. In the account which follows (Table I), it was found desirable to consider the response of the blood vessels in the finger to estrogen on the basis of these two groups. This was so since certain differences were found to characterize the dermovascular action of estrogen in each group.

The management of the patients was systematic. They were given estrogen twice weekly for the first 2 to 4 weeks, until some improvement in vasomotor symptoms was noted[1]. When some relief was obtained, the injection interval was increased to a week. With continued subsidence of symptoms, it was lengthened to 10 days, then to 2 weeks. From this time on, the injection interval was increased as the condition of the patient permitted. The results, from the standpoint of symptomatic relief, have been summarized in detail elsewhere (5) and so will not be reviewed here. In some cases, measurement of the dermovascular effects of estrogen could not easily be made, owing to extreme nervousness of the

[1]The hormones used in this work were generously supplied by various concerns as follows: Abbott, estrone, estriol; Ciba, estradiol, estradiol-dipropionate and testosterone-propionate; Parke Davis & Co., estrone; Schering Corporation, estradiol and estradiol-benzoate.

patient, especially at the outset of the treatment. In other cases, no attempt was made to record the response with each injection, but only at intervals of 4 to 6 weeks. Records were made during somewhat more than half of the estrogen injections. The technique of recording finger volume changes was exactly that employed by us before (5). The patient was comfortably seated in a room which was free from noticeable drafts. An arm rested on a pad just below the level of the heart, and a finger was inserted into a small glass finger plethysmograph. The only change from our previous procedures was that in this work the movements of the recording droplet were made on moving photographic paper. In the work on human males, readings were made of the position of the droplet in the pipette leading from the plethysmograph, and the curve of finger volume constructed from these readings. After a suitable initial control period in which the position of the droplet remained unchanged, injection of estrogen was made subcutaneously in the opposite arm or intramuscularly in the gluteal muscle. Upon completion of the injection, the light beam to the camera was interrupted, and the record thus marked. Minute intervals were recorded on the paper automatically by means of a suitable timing device. The records were continued for a half hour period, during which time the initial vascular action, if any, of estrogen may be observed. The character of the responses observed in these patients is noted below.

TABLE I.—FINGER VOLUME CHANGES AFTER INJECTION OF ESTROGEN IN MENOPAUSAL WOMEN. RECORDED BY MEANS OF A PLETHYSMOGRAPH.

Types of menopause	Condition of patient	Number of observations	Volume charge:	
			Before relief	After relief of symptoms
a. Psychogenic		(total)	%	%
D.T.	S	8		1.83
D.M.	S	18	1.82	1.36
V.I.	S	12		1.36
C.O.	S	18	1.75	1.62
J.N.	S	12	0.66	0.66
E.M.	S	22	2.00	2.00
M.D.	S	18	2.85	
R.W.	X-ray	12	3.63	1.25
E.P.	S	2		
M.diL.	X-ray	2		
F.B.	M	4	2.54	
	Average		2.18	1.38
b. Non-psychogenic				
S.L.	N	11	1.60	1.00
F.W.	S	12		1.38
A.N.	S	17	2.11	2.55
M.M.	N	9	3.66	2.22
H.K.	N	11	2.74	2.00
H.F.	S	10	2.15	0.92
	Average		2.04	1.68

S —surgical menopause
N—natural menopause
M—menstruating

RESULTS

Types of dermovascular response to estrogen. In Table I, it will be seen that any of three effects of estrogen on finger volume may be observed in menopausal women. They are, namely, a *flush type*, a *plateau type*, and a *negative* or undiscernible effect of the hormone. The last is self-explanatory. The plateau type of response is characterized, as in earlier work (5), by an increase in finger volume, commencing within a few minutes after injection of estrogen and progressing steadily to a maximum in the course of 20 to 30 minutes. During this time, there is no discernible elevation of skin temperature, as measured by a sensitive thermocouple (No. 30 gauge wire) and a Leeds & Northrop skin-temperature potentiometer. The flush type of response is superimposed upon a plateau response, and is marked by a sudden acceleration in the rate of finger volume increase, and by a measurable elevation of skin temperature of which the subject is aware. This is sometimes accompanied by sweating but seldom by a chill. The flush subsides after a period of 3 to 15 minutes.

The functional components in the two types of response are clear, partly on the basis of our past work (5) and partly on the basis of principles in physiology which are well established. The plateau type of response, noted in the earlier work (5), was held to be the result of vasodilatation beyond the arterioles. This conclusion stems first, from the fact that the vasodilatation is unaccompanied by any perceptible elevation of skin temperature (i.e., there is no significant increase in the rate of blood flow in the skin); second, from the fact that in the ear of the rabbit, the vessels which dilate under the action of estrogen are seen to be the smallest ones; and third, from the fact that under favorable circumstances, this vasodilatation in the ear of the

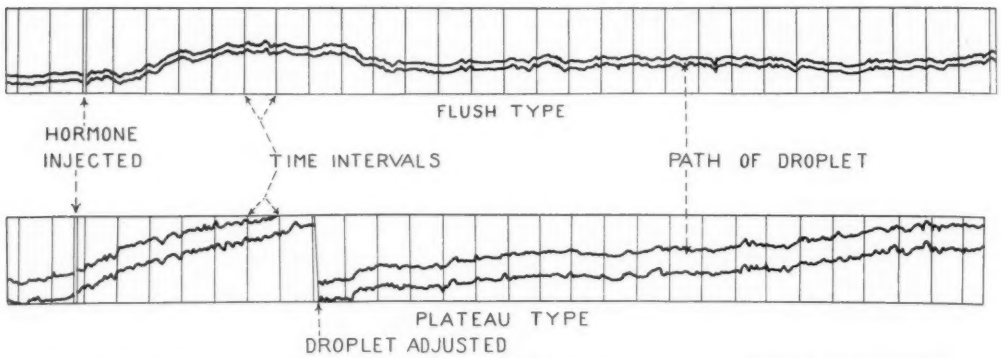

Fig. 1. Tracings which were made from continuous photographic records of flush type responses of the blood vessels in the finger to injection of estrogen (top tracing) and of the plateau type of response (bottom tracing). Plethysmographic records. The first is the result of a period of arteriolar dilatation superimposed upon a background of capillary dilatation. The plateau type is the result of capillary dilatation alone.

rabbit occurs at the same time that a decrease in skin temperature (i.e., arteriolar constriction resulting in diminished blood flow) takes place. Finally, recent plethysmographic measurements by Abramson and co-workers (personal communication) confirm the vasodilatation following injection of estrogen without concomitant increase in the rate of blood flow.

The flush type of response stands in marked contrast to the plateau type just described. In it, the vasodilatation is associated with increased skin temperature. This signifies a local increase in the rate of blood flow—an effect which can be accomplished most readily and most probably by arteriolar dilatation. Such a mechanism involves intermediation of central autonomic connections. This contrasts with the plateau type response which involves capillary blood vessels whose functional capabilities are not demonstrably altered by denervation (3). Such a difference between the 2 types of response constitutes, therefore, a significant point of contrast, and it enables one to draw certain inferences concerning the genesis of the menopausal flush on one hand, and of the mode of action of estrogen upon them, on the other. This is suggested by the incidence of the several types of dermovascular response seen during the course of treatment of the patients listed in Table I.

Frequency of the 3 types of responses. A glance at Figure 2 shows that the frequency of the flush, plateau, and negative responses varies according to, (a) the clinical condition of the patient, and (b) the presence or absence of neuroses as contributing factors to the menopause syndrome. This is exemplified by the following relationships.

Before clinical relief from the vasomotor disturbances of the menopause, flush type responses predominated. They occurred in 68 per cent of the responses seen in the group of neurotic patients, and in 40 per cent of those without a well defined neurosis. Negative responses were virtually nil. After clinical relief, however, plateau responses predominated and negative effects of estrogen were observed much more frequently. Both of these increases were at the expense of the flush type response, seen before there was clinical relief.

On the whole, therefore, clinical relief, whether afforded by hormone, suggestion, or other medication, brings about a decrease in vasomotor instability and in the responsiveness of the smallest blood vessels of the skin to the action of estrogen. The former is, of course, a well known fact among clinicians, but the latter effect has not been known. This decrease in responsiveness of the smallest vessels is attested further by the change in amplitude of the dermovascular response to estrogen, as shown below.

Quantitative aspect of the dermovascular responses. In Table I, the average percentage increases in volume of the finger after clinical

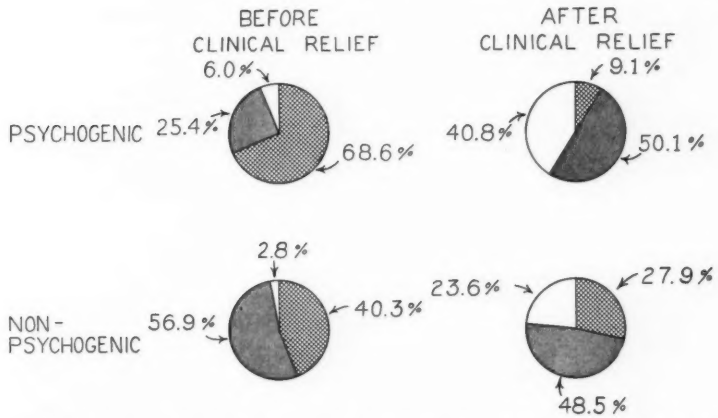

Fig. 2. Diagrams showing the incidence of flush responses, plateau responses, and of negative effects of estrogen on finger volume before, left, and after, right, clinical relief from the vasomotor disturbances of the menopause. At the top, data from women in whom psychogenic factors were largely responsible for the menopausal disturbances; at the bottom, from women in whom no important psychogenic factors were found. Cross hatch, flush response; vertical lines, plateau response; white area, negative.

relief are noted. These are based upon the plateau and negative responses only. Omission of the flush type response seems permissible since it consists of a different physiological mechanism involving arterioles and capillaries instead of capillary blood vessels alone.

It will be seen in the data summarized in Table I that both groups of patients showed, on the average, smaller responses to estrogen after there was clinical relief than before. The basis for this must be determined by further investigation.

Sex differences in the dermovascular action of estrogen. There are two outstanding differences between men and women in their respective dermovascular responses to estrogen.

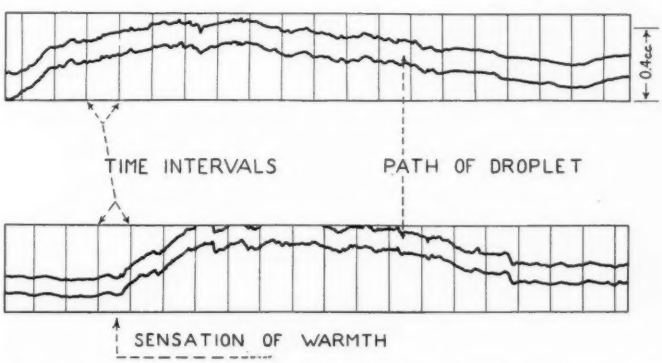

Fig. 3. Two examples of finger volume changes in spontaneous menopausal flushes, uncomplicated by estrogen. The one above lasted about 15 minutes, the one below largely subsided in 11 minutes. The sensation of warmth and suffocation is most noticeable during the rising phase, especially in the type of response in which the initial rise is very rapid. Sweating, when it occurs, is most obvious when the flush is at a peak. In neither of these flushes was there a sensation of chilliness; this follows with more rapid recovery, i.e., vasoconstriction, from the flush.

One is the amplitude of the response, the other, the types of responses seen in the two sexes. In men, the average increase in finger volume was 4.6 per cent, in women, after clinical relief, 1.5 per cent, although negative responses comprised a considerable proportion of the responses.

A more striking difference between men and women, however, was the fact that in no male was a flush type of response observed, whereas it was seen, even after clinical relief, in women. It is possible, of course, that an age difference between the two sexes may account for the variations noted, since the men, for the most part, were in the third decade of life whereas all but two of the women were in the fourth and fifth decades. The two exceptions were 26 and 27 years old. The women, moreover, clearly suffered from a well defined endocrine dyscrasia which the men did not. Consequently, a sex difference in the dermovascular action of estrogen is suggested, rather than demonstrated, by these experiments. As they stand, however, the data clearly show that in the 2 groups of men and women with whom we have worked, the capillary blood vessels in men are more sensitive to the action of estrogen than are those of menopausal women who have experienced clinical relief from their symptoms. The reasons for, and significance of, these facts remains to be established.

The menopausal flush versus the dermovascular flush with estrogen. The question arises of the relationship between the flush type of response which we have frequently observed and the natural flush of the menopause, uncomplicated by estrogen. Records have been made during several such flushes, examples of which are shown in Figure 3. It will be seen from these that the menopausal flush resembles qualitatively that of the estrogen induced flush shown in Figure 1. It rises quickly to a maximum; it subsides quickly, and it lasts for a period of 10 to 15 minutes. The last feature of the flush is interesting inasmuch as the patient notices,—and minds,—the flush in the early, rising phase. This is a period of rapid rise in skin temperature. At the height of the flush, sweating may occur, and this in turn may be followed by a sensation of coldness. When this is marked, decrease in finger volume, i.e., vasoconstriction, takes place more rapidly.

The chief difference between the natural flush and the estrogen induced flush is that the latter is slower to develop and subside. Correlated with this is the more intense sensation in the natural than in the estrogen induced flush. This difference may be explained most readily by the fact that the more rapid the rate of influx of warm blood into the skin, the more rapid will be the rate of stimulation of the warm receptors in the affected area, and, consequently, the more intense will be the sensation of heat and suffocation.

All in all, therefore, the difference between the natural and the estrogen induced flush appears to be one of degree. The basic physiological mechanism of each is heightened sensitivity of centers in the nervous system to otherwise inadequate stimuli. The relative abatement of the flush type of response to estrogen with clinical improvement, and the absence of flush type responses to estrogen in the group of normal males that we have studied (4), both testify to the correctness of this conclusion. It follows accordingly that the essential physiological disturbance in the menopausal flush involves a primary endocrine dyscrasia coupled with psychic or somatic factors playing upon the peripheral vascular tree, affecting the innervation of the smaller arterioles of the skin on one hand, and the irritability of the contractile elements of the blood capillaries themselves, on the other. Other contributing factors, if such may be involved, remain to be established.

SUMMARY

1. There are two different dermovascular effects of estrogen observed in menopausal women. These are measurable by means of a finger plethysmograph. They are: (a) A slow, progressive increase in the size of the finger, commencing immediately after intramuscular injection of the estrogen. This is called a plateau response. (2) While a plateau response is developing, a sharp increase in finger volume may occur which reaches a maximum level where it is sustained for 3 to 15 minutes, and then subsides appreciably to

a point somewhat above the preinjection level. This has been called a flush type of dermovascular response.

2. There are two important differences between plateau and flush type responses. With regard to skin temperature, no change is observed in the plateau response, whereas there is an elevation of temperature in the flush type response. There is no significant change, therefore, in blood flow in the former response, whereas there is in the latter. With regard to sensation, there is none definitely associated with the plateau response. With the flush type of response there is a feeling of warmth during the initial phase of the flush, as warm blood apparently rushes into the skin. In this, therefore, there is arteriolar dilatation, whereas the plateau response involves blood vessels lying beyond the arterioles.

3. The relative frequency of these responses in menopausal women is affected by the clinical condition of the patient at the time of injection. Before relief, the flush type of response predominates; after clinical relief, the flush type response diminishes in frequency, and the plateau response increases somewhat. In a significant number of instances, no dermovascular action of estrogen is demonstrable.

4. These changes in the relative frequency of the dermovascular responses were most marked in women whose menopausal condition was relieved through removal of a complicating neurosis, and least marked in those women in whom no psychogenic factor was discovered.

5. The results recorded may be regarded as objective evidence of increased stability of the vasomotor nervous centers (by diminished number of the flush, or arteriolar dilatation responses), and of the capillary blood vessels (by increased frequency of injections which are not followed by definite dermovascular effects).

6. It is concluded that clinical improvement in the vascular disturbances of the menopause brings about certain adjustments of a stabilizing nature on the peripheral vascular tree, affecting both the arterioles of the skin, and the capillary blood vessels. The extent of this relief is more marked when a complicating neurosis (psychogenic factor) that may be present is removed, and less marked when the menopause is primarily somatogenic in origin.

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DIVERTICULAR INGUINAL HERNIA

CLAUDE C. BURTON, M.D., F.A.C.S., and CARL BLOTNER, M.D., Dayton, Ohio

LITTLE is found in the literature concerning diverticular inguinal hernia. Our attention was first directed to diverticula as an entity by Andrews and Bissell in 1934. Since that time we have kept constant vigil for this type of hernia, carefully recording the operative findings in 2,302 primary hernial repairs performed from January 1, 1935, to June 1, 1940. During the hernia operations, the sac with its attendant accessory locules has been dissected from adjacent structures of the floor of the canal, identified, mobilized, and the relative merit of the muscular and fascial tissues as a stratum determined. Notations were made of the type of diverticulum—whether communicating, noncommunicating, or fatty—and its relation to the direct or indirect sac, the fascia transversalis and the inguinal ligament.

A review of the literature on herniology indicates a lack of fulness of understanding in regard to the inguinal diverticular locule. Diverticula, either because of their rarity or failure of recognition by the general surgeon, have not received the attention they deserve. This conclusion is supported by data submitted in this report and by an analysis of 130 recurrent hernias made by one of us (C. C. B.).

Our purposes in this paper are to determine the incidence of diverticular hernias in a representative series of primary hernias, their type, the relationship to the coexisting sac, and the follow-up statistics, including the percentage of recurrence in 62 primary and 33 recurrent hernias with diverticular locules. Moreover, it is proposed that if this characteristic hernial outpouching or variant occurs with sufficient frequency and plays a rôle important enough, consideration should be given it in regard to its classification as a type of hernia.

Perhaps the incidence of diverticular hernia in this series is high. This may be attributed to (a) the age group with which we are dealing, namely fifth and sixth decades; this age represents the period of beginning decline with diminution of muscle tone, fatty degeneration, and increased tissue friability, the fascia developing a propensity toward the formation of rents; (b) a more thorough mobilization of all locules of the sac; and (c) our enthusiasm or hernia-mindedness. Since the incidence of diverticula was 13.8 per cent in a series of 130 recurrent hernias, ranking third in the type of sac found, speculation was aroused as to the frequency of diverticula in primary hernias. In searching the literature for the answer, we failed to find any reports on this particular type of hernia save that of Andrews and Bissell, and therefore decided to analyze our own series. It is hoped that others will do likewise and by the accumulation of statistical data, we may be able to arrive at a more accurate incidence.

Possibly some members of our profession may wonder why it is necessary to go into the dissection of these seemingly insignificant hernial locules or variants of the major sac so minutely beyond any apparent practical importance they may have, thus making a relatively simple procedure more complicated and confusing without achieving any notable results other than the removal of these secondary outpouchings and the more elaborate repair. Carefully compiled follow-up statistics show an incidence of recurrence of from 5 to 10 per cent in primary indirect hernias, and from 10 to 20 per cent in direct hernias. In the case of recurrent or secondary hernias, the percentage of recurrence is even higher. It should be noted that the lower figures, as a rule, were obtained in instances of inadequate follow-up. Any surgeon with the impression that his results are superior will become mellowed by a careful survey of his cases carried as long as 5 years. The introductory statement by Seelig, in one of his articles published more than a decade ago, "The modern operation for the cure of inguinal hernia is not as satisfactory as we have grown accustomed to believe," is no less true today. Page, of London, reexamined 206 patients, whose average age

From the United States Veterans Administration.

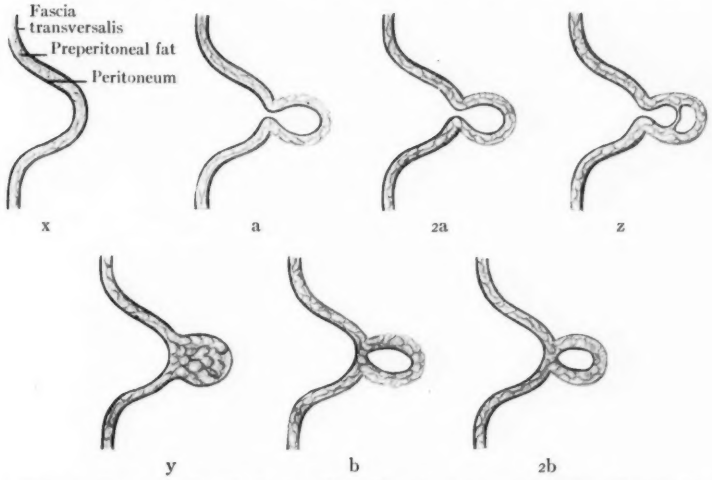

Fig. 1. Types of diverticula. x, Direct hernia; a, communicating diverticular hernia without fascia transversalis; 2a, communicating diverticular hernia with fascia transversalis; z, multilocular diverticular hernia with communicating and noncommunicating locule; y, fatty diverticulum; b, noncommunicating diverticular hernia without fascia transversalis; 2b, noncommunicating diverticular hernia with fascia transversalis.

was 31, from 5 to 9 years after operation. The recurrence rate for indirect hernia was 20.29 per cent and for direct hernia 25.2 per cent. Andrews and Bissell, in their collective analysis of 13 authors, found an average recurrence rate of 20 per cent for direct hernias. These published reports reflect the work of our most experienced and trustworthy surgeons, employing various types of hernioplasties most of which have been in use a decade or longer. Therefore, it would seem that the consensus of most herniologists points to a high incidence of recurrence of inguinal hernia, more particularly the direct type which is usually repaired by the ordinary hernioplastic procedure. This is indicated by every report in which the ultimate results are meticulously scrutinized. Under these circumstances, the most minute anomaly or variant of the sac or wall of the inguinal region may be an important factor in recurrence and is worthy of our ingenuity and best efforts to the end that a more substantial repair may be attained. Uppermost in this era of hernia repair has been the emphasis on the mobilization and exclusive utilization of the all important fascial wall. As expected, with continued progress there have been modifications in the technique but in the main, these modifications have not deviated from the fundamental principles for the achievement of fascial apposition laid down by Gallie and LeMesurier, Koontz, Wangensteen, McArthur, Zimmerman, and many others.

In contrast with the wall, the sac in recent years has not received comparable attention. In detailing the summary of our findings in regard to the morphology of the sac, frequently we were unable to classify the type of sac at hand. It was noted that the conventional classification had been applicable to hernias that had developed to some size, rather than to those noted in their incipiency.

Parsons, in 1937, referred to the indirect-direct type of sac, thus initiating a trend toward classification of inguinal hernia from the standpoint of the position and location of the locule or locules. This seemed to us more accurate and therefore gave impetus to more careful saccular as well as mural dissections. Burton and Ramos used locular division of the sac in their analysis of 130 recurrent hernias. We propose to continue the use of the sac locule as the basis for classification of inguinal

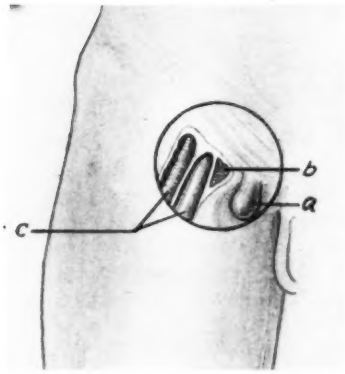

Fig. 2. *a*, Unusual type of diverticular locule emerging beneath the inguinal ligament between the femoral canal and spine of the pubis; *b*, femoral canal; *c*, femoral vessels.

hernia: (1) monolocular, which may be either indirect or direct, but preponderantly the former; (2) bilocular, or combined indirect-direct which is more prone to occur in those of the fifth and sixth decades; (3) trilocular, or indirect-direct-femoral, more likely to develop where there is marked structural weakness (these are usually huge and recurrent); (4) sliding, which is unilocular, but so unlike any other type that it would be more confusing to change its present identity; (5) diverticular hernia.

DEFINITION

A diverticular hernia is a small, pear or sausage-shaped protrusion of peritoneum, or occasionally, fat, coming through a rent in the fascia transversalis. At times the margins of the rent are quite clearly demarcated. Occasionally a funnel-shaped protrusion is formed, presumably due to adherent, attenuated fascia, forming one of the sac coverings. The varying thickness of the coverings and the appearance of the rent have given credence to the theory that the fascia does not bear a constant relationship to the hernia. These endothelium-lined outpouchings of peritoneum are, as a rule, empty, with the exception of the rare fatty ones, which are made up exclusively of smoothly rounded, firm lobules of fat, with very thin connective tissue capsules. The diverticula are usually of uniform size, 3 to 4 centimeters long with a fundus measuring 2 centimeters in diameter and neck approximating 1 to 1.5 centimeters. They arise most commonly as off-shoots from the direct sac or direct locule of the bilocular sac (87 per cent), and usually from the inferior and mesial aspect of its dome, although they may occur independently (Fig. 3).

ETIOLOGY

The exact cause of these diverticula, as in the case of diverticula elsewhere, is not known. The existing difference of opinion in regard to the origin of these divers outpouchings attests to their confused etiological status. Many theories have been advanced for the origin of bladder, intestinal and other diverticula concerning which mention has been made of congenital, traumatic, and acquired sources. Muscular and fascial weaknesses subjected to strain, and the effect of normal processes on tissues which have developed abnormal characteristics have also been considered etiological factors. Since there is no vestigial remnant in the inguinal region which might explain their source, one must look elsewhere. The congenital source of hernia is well recognized. The absence of perisaccular and peridiverticular adhesions would tend to eliminate traction as a cause of diverticular development. By exclusion, then, one may regard increased pressure from within as the precipitating factor in the causation of diverticular hernia. In other words, the traumatic pulsion theory is proposed.

CLASSIFICATION

Diverticular hernia may be of 3 types: communicating (Fig. 1, a), noncommunicating (Fig. 1, b), and fatty or adipose (Fig. 1, y). In our series of 62 diverticular hernias, there were 38 communicating, 21 noncommunicating, and 3 fatty.

The communicating diverticulum consists of a direct extension of the peritoneum through a small, constricted aperture in the posterior wall of the canal, with a narrow isthmus or stalk, perhaps not any larger than the diameter of a lead pencil leading into the bulb-like fundus. Sometimes the tip of the finger can be inserted into the locule from within the abdomen, which facilitates its dissection from

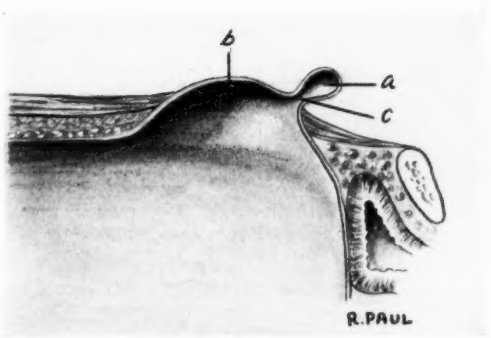

Fig. 3. *a*, Communicating diverticular hernia springing from the dome of a direct sac; *b*, direct sac; *c*, note the narrow neck of the diverticular locule contrasted with the wide neck of the direct sac.

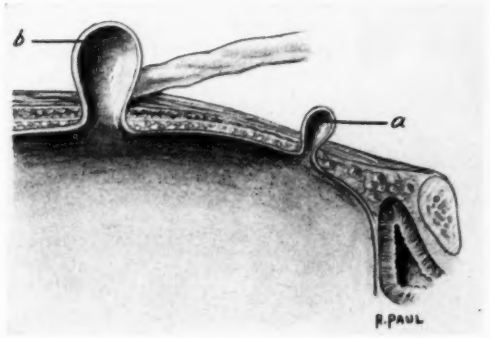

Fig. 4. *a*, Communicating diverticular locule arising independently of the indirect sac. *b*, Indirect sac.

adjacent tissues and occasionally from the bladder wall. This is a concrete illustration of the value of careful digital exploration of the entire sac and undersurface of the floor of the canal to prevent overlooking any variant of the sac or adjacent peritoneum. The locules may contain a wad of omentum which in a few instances has become incarcerated, but no bowel has yet been found within the diverticulum. Owing to the narrowness of the communicating channel, the chances of gravitation of a knuckle of bowel through this opening seems very unlikely.

The noncommunicating and communicating diverticula are structurally identical with one exception. In the former the orifice of the diverticulum has become obliterated, leaving a closed, empty, oval locule. This type of diverticulum could be very easily overlooked during the dissection of the sac. It is usually asymptomatic, and on careful examination of the canal one might elicit a small, irreducible lump; this provides for a clinical setting leading to a diagnosis of hernia, with grounds for nonacceptance industrially. Or, in the event of previous repair, these findings might be interpreted as a recurrence, when in reality, the diverticulum had been overlooked at the time of the original hernioplasty. This has occurred in 26 instances in our series.

Prior to the time we began saving and studying some of the excised diverticula in collaboration with the pathologist, we considered them all unilocular. However, on section of some of the specimens after they had been fixed, we found one which was bilocular, the proximal locule communicating with the peritoneal cavity and the distal locule completely closed, but superimposed on the former. The combined protrusion produced a coexisting, communicating and noncommunicating diverticulum, (Fig. 1, z).

A fatty diverticulum is a spherical, smooth, encapsulated, solitary, nonreducible mass of firm, rubbery consistency, containing packed miliary lobules of fat and making its exit through a slit in the fascia transversalis in the inguinal triangle. It is unrelated to the sac or peritoneum. In this series, it occurred three times, the incidence being 4.8 per cent. This type of diverticulum is more prone to develop if there is considerable fatty degeneration and if the fascia transversalis has become thin and friable, predisposing to a tear when subjected to stress. It is a rare collateral finding in the inguinal area which, when found, should be excised with closure of the rent for the sake of completeness of the repair. Furthermore, this removal forestalls the chance of erroneous interpretation as a recurrence on later examination. An adipose diverticulum should not be confused with lipomas of the cord, which bear no immediate relation to the sac.

DIAGNOSIS

An accurate preoperative diagnosis of diverticular hernia cannot be made. In this respect it is similar to sliding hernia, which

TABLE I.—TYPES OF COEXISTING SACS

Type	Communicating	Noncommunicating	Fatty
Direct	36	18	3
Indirect	2	3	0
Associated with recurrent direct sacs	14	20	2
Side of occurrence—			
Bilateral	2	2	0
Right side	27	11	2
Left side	11	10	1

cannot be identified as such until exposed at operation. In fact, we question the accuracy of the preoperative differentiation of indirect and direct hernias. Andrews and Bissell described and illustrated methods for their differential diagnosis, and Harris and White stressed the importance of the length of the inguinal ligament in the differentiation between direct and indirect hernias. In our experience these diagnostic maneuvers have not been successful, perhaps because of the high incidence of combined indirect-direct hernias in the age group with which we are dealing.

However, there are clinical settings which are very suggestive of diverticular hernia. The presence of a small, rather firm, irreducible bulging, about 2.5 centimeters in diameter, which transmits no impulse or a faint impulse, and, with no palpable or a dwarfed defect in the posterior wall of the inguinal triangle, is strongly suspicious of a diverticular hernia. Since a diverticular hernia rarely exists alone, the chances of a reasonably accurate preoperative diagnosis are rather remote. On the other hand, the diagnosis of such a hernia at operation is again, like sliding hernia, quite simple, as has been pointed out heretofore.

The differentiation of the diverticulum from the major sac in the communicating type is made by its size, location, and small hiatus.

TABLE II.—OPERATIVE PROCEDURES IN DIVERTICULAR HERNIAS

	Primary	Recurrent diverticula*
Routine repair	58	19
Fascial suture, Gallie or McArthur	2	13
Cooper's ligament, Dickson	2	0
Pedicle graft, modified Wangensteen	0	1
Total	62	33

*Only recurrent hernias with associated diverticular locules included.

TABLE III.—FOLLOW-UP STUDIES

Time in mos.	Communicating	Recurrent	Noncommunicating	Recurrent	Fatty	Recurrent
3 to 12	11	1	7	0	3	0
13 to 24	18	3	6	1	0	0
25 to 36	4	0	2	0	0	0
37 to 48	2	0	4	0	0	0
49 to 60	3	0	3	0	0	0
Total	38	4	22	1	3	0
Examined by physician	28	3	13	1	3	0
Letter contact	9	1	6	0	0	0

The narrow, constricted neck never spreads or becomes dome-like, but maintains its original form after complete dissection of the sac. In fact, it is as clearcut an entity and is as easily distinguishable as a diverticulum of the bladder, with which it shares many identical characteristics. We have yet to find a diverticulum of an indirect sac, but the two may coexist (Fig. 4), the former remaining entirely unrelated to the sac. Of these there were 5 instances, or 8 per cent in this series. We have had 1 case (Fig. 2) in which the hernia was diagnosed as femoral. However, at operation this was found to be a diverticulum which had insinuated itself under the inguinal ligament between the femoral ring and Gimbernat's ligament, thereby remaining deep to the fascia transversalis and thus producing a variant in which the diverticulum did not pass through a slit in the fascia transversalis.

TREATMENT

In the event the diverticulum constitutes the only departure from normal, it should be excised, the stump ligated, and the tear in the fascia transversalis sutured. However, since

TABLE IV.—FURTHER FOLLOW-UP STUDIES

	No.	Per cent
Diverticular hernias in 2,302 primary hernias	62	2.6
Recurrences in 62 primary diverticular hernias	4	6.4
Recurrences in 33 recurrent hernias associated with diverticular locules	4	12.0
Diverticular locules in 130 recurrent hernias.	18	13.8*

The strikingly higher incidence of diverticular locules in recurrent hernias as compared with primary hernias would indicate that the locules are being overlooked in the original repair.

*Surg., Gynec. & Obst., 1940. 70: 969-975.

the diverticulum is almost invariably concomitant with saccular and mural abnormalities, its treatment is that of the basic major weaknesses. The suitable operative procedure, therefore, may vary from the simple routine repair to the most radical hernioplasty. A summary of operative procedures used in 62 primary and 33 recurrent diverticular hernias is given in Table II. In the former, routine repair, which includes excision of the sac and diverticulum, with transposition of the cord, was done in 58 cases, or 94 per cent. In 2 instances, fascial sutures were employed, and in 2 the fascia transversalis was sutured to Cooper's ligament. In the recurrent diverticular hernias, as one would expect, the diverticula are more difficult to expose and require more formidable procedures. Routine repairs were performed in 18 cases, or 56 per cent, fascial sutures in 13 cases, or 40 per cent, and pedicle graft in 1 case, or 3 per cent. The incidence of recurrence in 62 primary diverticular hernias followed from 3 months to 5 years has been found to be 6.4 per cent (Table III). Most of these repairs were of 2 years' duration. In the diverticular recurrent hernias, the incidence was 12 per cent.

CONCLUSIONS

1. Data are presented showing the incidence of diverticula in 2,302 primary hernias.

2. The presumptive clinical manifestations for making preoperative diagnosis and the characteristic findings at operation are discussed.

3. The relation of the diverticulum to the coexisting sac in 62 primary and 33 recurrent hernias with diverticula is summarized.

4. Comparison of incidence of diverticula in primary and recurrent hernias is 2.6 per cent and 13.8 per cent, respectively, warranting the assumption that diverticula are overlooked at the time of the initial repair.

5. A classification of inguinal hernias on the basis of the locule and of diverticular locules is proposed.

6. The operative technique used in the primary diverticular hernias and in the recurrent hernias with diverticula in this series is detailed with follow-up studies, showing a recurrence of 6.4 per cent in the former and of 12 per cent in the latter.

NOTE: Published with the permission of the medical director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

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URINARY EXTRAVASATION (PERIURETHRAL PHLEGMON)

Pathogenesis and Experimental Study

EDWARD O. FINESTONE, M.D., New York, New York

CONFUSION still exists with regards to the pathogenesis of urinary extravasation; or, as it is more recently termed "periurethral phlegmon." Two theories have been advanced to explain this important and serious phenomenon: (1) The older notion subscribed to the belief that urine actually was "squeezed" out into the tissues through a defect in the urethra. (2) The newer conception explains the picture on the basis of bacterial invasion, chiefly by anaerobes.

Briefly, these two concepts can be labelled: (1) the hydrostatic theory, and (2) the theory of bacterial invasion. There is no doubt that ultimately bacteria and their products are responsible for the varied clinical manifestations of urinary extravasation. However, the question arises as to whether the extravasated urine itself dissects the fascial planes or the bacteria (chiefly anaerobes) produce the invasion. Although this question appears to be academic, an attempt at its solution has led to a newer concept of the pathogenesis and, therefore a more rational method of treatment.

According to Hinman "Three types of urinary extravasation are commonly encountered: (1) between the layers of Buck's fascia from the pendulous or bulbous urethra; (2) within the superficial perineal pouch below the urogenital diaphragm from the bulbomembranous urethra, or from the membranous urethra with rupture of the superficial (inferior) layer of the triangular ligament; (3) above the urogenital diaphragm, from the prostatic urethra or from the membranous urethra if associated with rupture of the superior fascia of the urogenital diaphragm."

Of these three types the second is the commonest and it is the one which is concerned in this study. Presuming a defect in the bulbomembranous urethra, the extravasated urine would extend beneath Colles' fascia, into the perineum in front of the inferior fascia of the urogenital diaphragm. The attachments of Colles' fascia are such that the fluid must extend forward beneath the dartos of the scrotum and penis, and thence up over the abdomen beneath Scarpa's fascia. It may extend as high as the axilla. The urine cannot spread laterally or posteriorly because of the connection of Colles' fascia with the pubic rami and the inferior layer of the urogenital diaphragm. Its spread on the thighs is limited by the fascia lata. Figure 1 (modified after Wesson) demonstrates the various paths of urinary extravasation.

From the Surgical Service of Dr. Joseph B. Stenbuck at the Harlem Hospital, New York, New York.

Exhibited at the Graduate Fortnight at the New York Academy of Medicine, October 14 to 26, 1940.

No recent experimental work on extravasation has been reported except that of Bezza. Working with rabbits, he was able to reproduce the clinical and bacteriological features of extravasation by sectioning the ureter or wounding the bladder.

In seeking confirmation for the hydrostatic theory, the present study was undertaken. If the phenomenon of extravasation were purely hydrostatic, it should be possible to reproduce the clinical appearances by injection experiments. This was first attempted by Wesson (21) who is quoted as follows:

> "To determine the extent of Colles' fascia anterior to the suspensory ligament, under inspection through an endoscope, the urethra in fresh cadavers was punctured by means of a long needle, and colored fluid was injected so as to simulate a rupture of the urethra. Ventral ruptures of the bulb formed a circumscribed lump in the perineum, but with increased injections the fluid gradually spread, evidently passing between the connective tissue partitions. When the force was still further increased, these partitions gave way, and one side of the scrotum became filled. Extending the amount of the fluid still further caused extravasations to rise toward the symphysis, but when its passage in that direction was prevented by means of pressure over the pubic bone, the fluid passed down into the penis between Colles' and Buck's fasciae, demonstrating the continuity of Colles' fascia into the penile organ."

To add to Wesson's work, the following factors were considered and deemed advisable: (1) It was not necessary to work through an endoscope, since, ultimately, the end of the needle would have to be introduced into the fascial planes; and the position of the distal end of the needle would determine the site of the extravasation rather than the place where the urethra was traversed. The procedure is blind in either event. Therefore, it was considered to be much easier to introduce the needle directly through the tissues of the perineum, seeking to gain the superficial perineal pouch. (2) In addition to the use of colored fluids, which might be identified by dissection, radiopaque material could be employed to make x-ray

demonstrations. (3) The quantities of fluid injected, the specific gravity, and the hydrostatic pressures required to produce progressive infiltration could all be measured. (4) Although Wesson makes mention of the progressive involvement of the scrotum, following the initial distention of the perineum, he is not clear about the layer which is infiltrated.

All writers on this subject indicate the Colles' fascia is continuous anteriorly with the dartos layer of the scrotum and penis. This is a very important point. From a surgical standpoint, if extravasations passed only beneath the dartos, only superficial incisions would be necessary to drain them. However, if extravasations invaded the deeper structures and the tunica vaginalis testis, deeper incisions would be required. Campbell (6), who has had an extensive experience with extravasation, has stressed the importance of widely and deeply incising the scrotal sac, to such an extent, that the completion of the operation finds the testes and spermatic cords completely exposed, "swinging free," bare, and later, retracted over the lower inguinal regions. If it could be shown that extravasated urine anatomically does not invade the deeper structures or the tunica vaginalis testis, such a radical procedure would be unnecessary and detrimental.

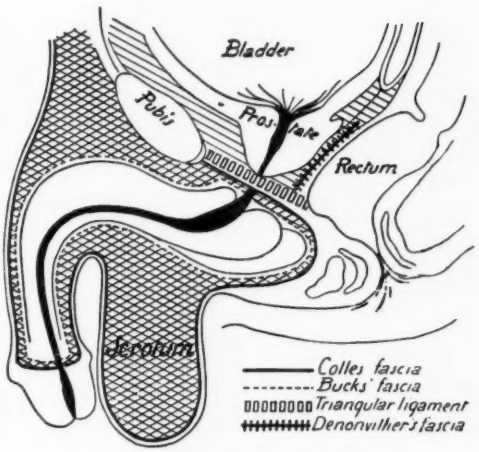


Fig. 1. The fascial planes concerned in urinary extravasation. Cross hatched area represents infiltration below the urogenital diaphragm, whereas obliquely shaded area represents infiltration above the urogenital diaphragm (after Eisendrath and Rolnick).

In the minds of those (6, 12, 18), who advocate diversion of the urinary stream, besides multiple incisions, in the treatment of urinary extrav-

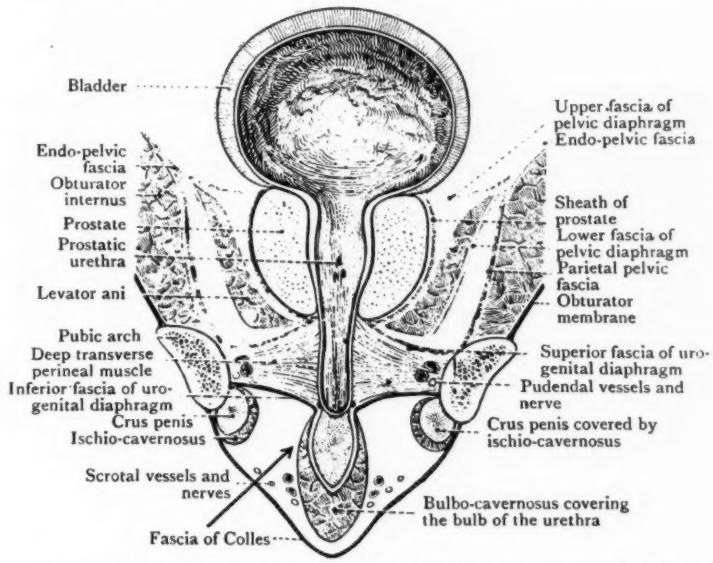
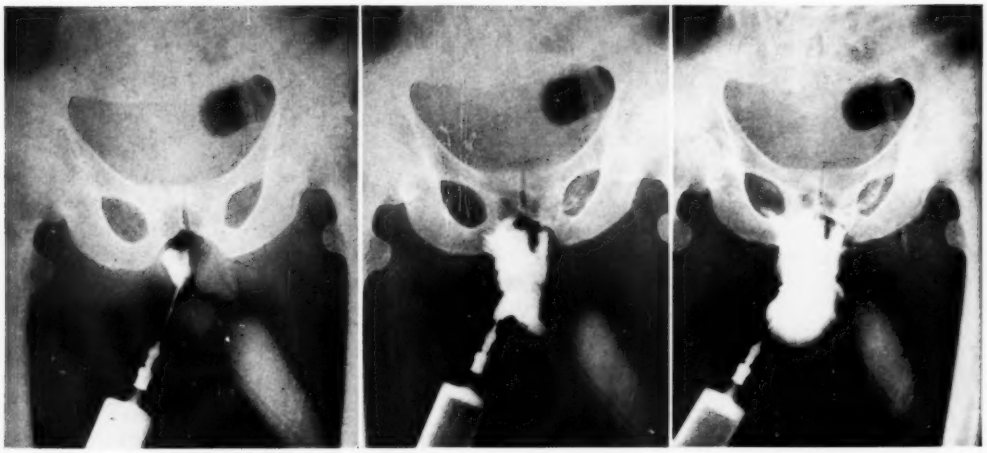


Fig. 2. Vertical transverse section through pelvis showing endopelvic fascia and Colles' pouch. The arrow entering Colles' pouch represents the direction and space approached for injection experiments. Note the proximity of the vascular bulb to the urethra and the surrounding bulbocavernosus muscle (after Cunningham).



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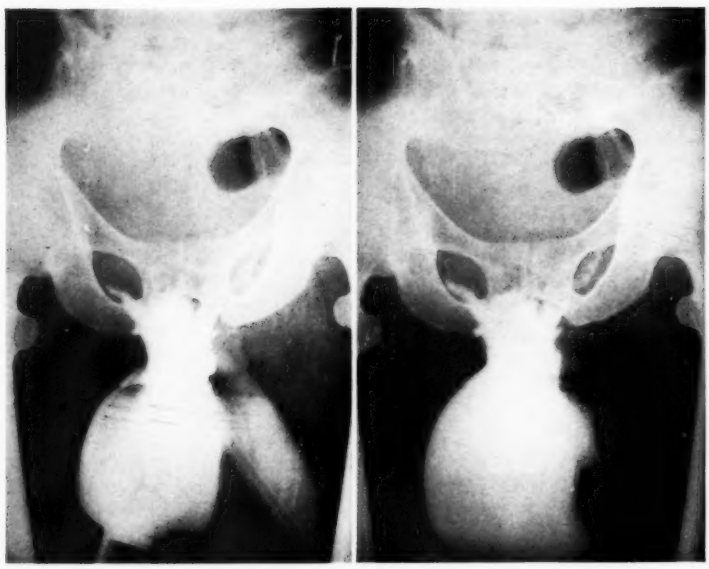

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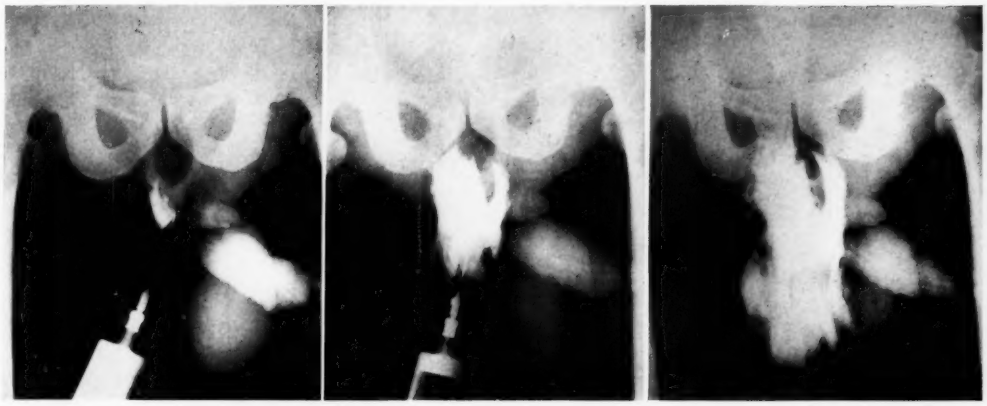
Fig. 3. a, Note calcified iliac and femoral vessels, catheter in urethra, needle in perineum, where 3 cubic centimeters of iodide have been injected. b, After injection of 50 cubic centimeters the perineum is filled and there is beginning extension over the postero-inferior aspect of the scrotum. c, After injection of 150 cubic centimeters perineum completely filled, scrotum symmetrically distended mildly. Two inguinal projections represent infiltrations along spermatic funiculi. d, After injection of 250 cubic centimeters the perineum remains the same, but there is progressive distention of the scrotum. e, After injection of 350 cubic centimeters perineum still the same; and greater distention of scrotum. *No penile or abdominal involvement* is seen in any of the films of this series.

asation, the rationale was to prevent more urine from being squeezed out into the tissues. On the basis of this reasoning many surgeons have failed to divert the urinary stream when stricture or retention was absent. In fact, many prominent urologists (14, 15, 16) do not mention this pro-



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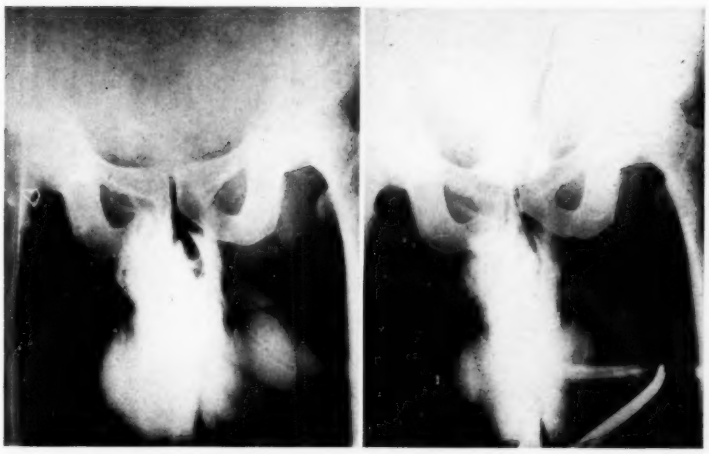

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Fig. 4. a, Note ascites, marked edema of penis and scrotum before injection, and needle in perineum, where 3 cubic centimeters have been injected below the bulb. b, After the injection of 50 cubic centimeters the perineum is filled and the fluid surrounds the root of the penis and starts down the scrotum. c, After injection of 150 cubic centimeters the perineum is filled to the same extent, but only half of the edematous scrotum is infiltrated. d, After injection of 250 cubic centimeters the perineum still remains the same, the scrotum is two-thirds infiltrated and the groins are slightly involved. e, After injection of 350 cubic centimeters the scrotum is almost filled, the groins are more involved and a few ounces of iodide in the bladder show its position. No penile or abdominal involvement is seen.

cedure. The omission of urinary diversion has led to an unwarranted and high mortality. Even those who practiced diversion could not reasonably explain this procedure in patients who were obviously voiding well and presented no stricture.

INJECTION EXPERIMENTS

Fresh male cadavers in which the pelvis, perineum, and genitalia were undamaged were selected for the following experiments: A preliminary x-ray film was made demonstrating the scrotum and penis prior to injection. The urethra was outlined by a silk woven catheter. A No. 20 needle penetrated the right side of the perineal triangle (Fig. 2) and was advanced for a distance of about 1½ inches. An attempt was made to retain the needle in the same position throughout the injection. A few cubic centimeters of the

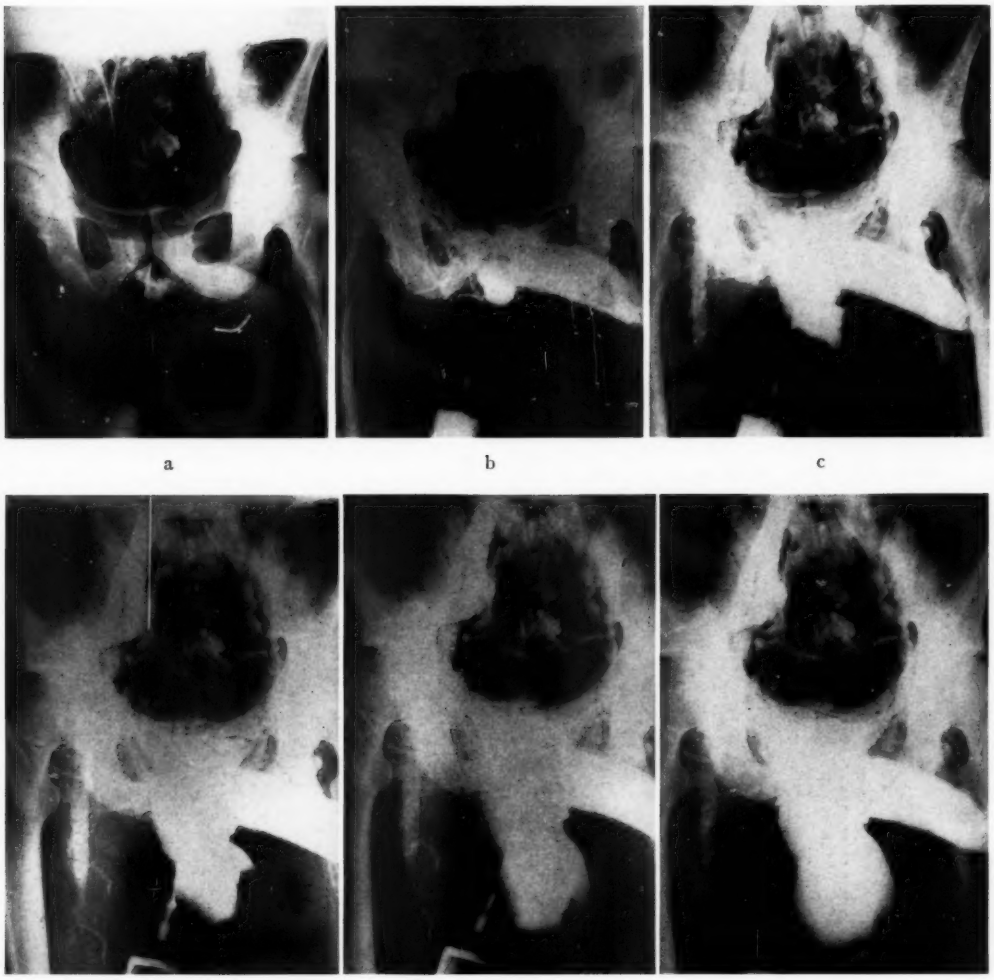

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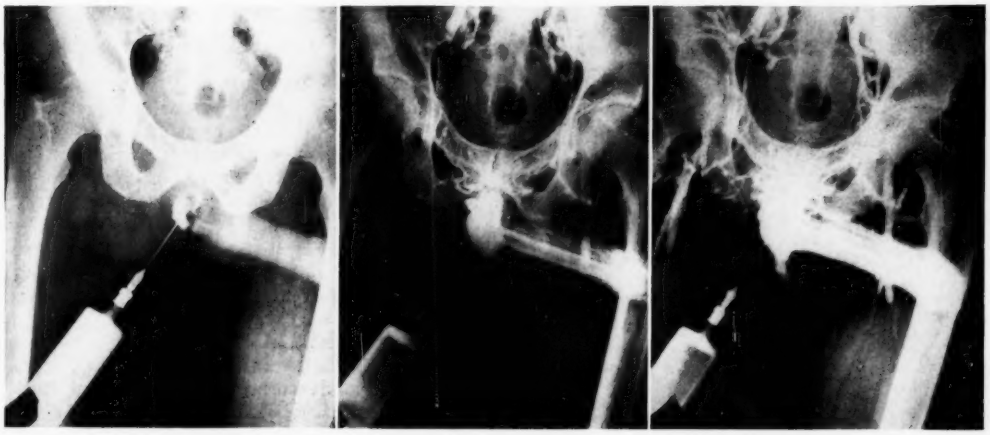
Fig. 5. a, Note inadvertent entry of bulb and initial injection of 3 cubic centimeters. b, After injection of 150 cubic centimeters bulb well outlined, but no perineal infiltration, because fluid permeates vessels of perineum, penis and pelvis. c, Needle slightly withdrawn; 200 cubic centimeters injected. Perineum now filled. Fluid starts down the scrotum. Cavernous bodies and penile vessels so thoroughly filled that the penis is one dense mass. d, After injection of 300 cubic centimeters there is progressive scrotal distention. e, After injection of 400 cubic centimeters there is further scrotal distention. f, After injection of 500 cubic centimeters scrotum completely filled, but not as greatly distended as in series 1 and 2, because most of fluid escaped into the vascular tree.

radio-opaque solution (10 per cent sodium iodide) were then injected and another x-ray film taken to demonstrate the position of the end of the needle and the site of the initial infiltration. Thereafter, injections were made of 50, 150, 250, 350 and 450 cubic centimeters, and at each increment the physical condition was noted and another x-ray film exposed.

By means of a manometer the pressure reached during the injection period was measured and it was maintained at between 60 and 80 millimeters of mercury.



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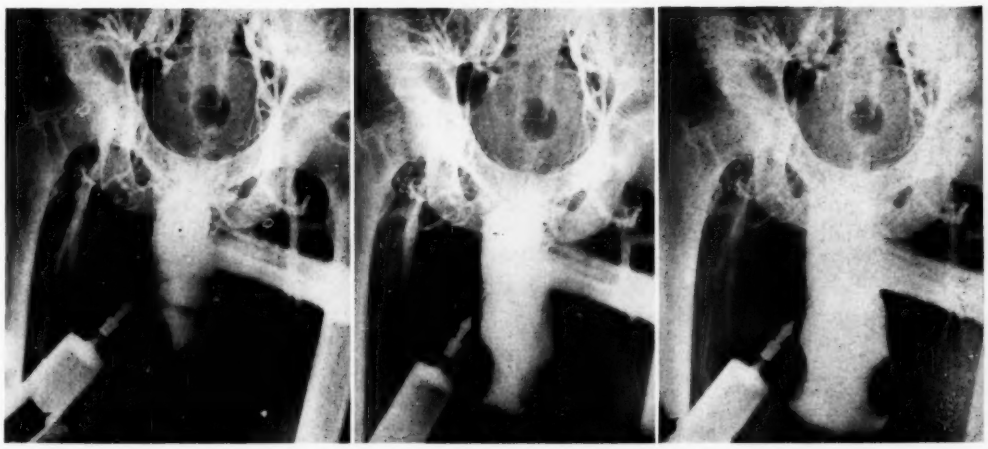

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Fig. 6. a, Initial injection of 3 cubic centimeters into perineum with involvement of bulb. b, After injection of 100 cubic centimeters, bulb and perineum outlined. Permeation of corpus spongiosum to glans penis. Perineal and pelvic vessels filled. c, Needle slightly withdrawn; 200 cubic centimeters injected. Perineum filled. Beginning extension to scrotum. Corpus spongiosum more densely outlined. d, After injection of 300 cubic centimeters there is progressive scrotal infiltration. e, After injection of 400 cubic centimeters there is further scrotal distention. f, After injection of 500 cubic centimeters the scrotum is filled. Concave indentations represent the sites at which the scrotum rested upon thighs, and do not picture the testes.

Nine cadavers were injected by this method. The first case is typical of extravasation beginning in the superficial perineal pouch, derived from rupture of the bulbomembranous urethra. The first roentgenogram (Fig. 3a) demonstrates the calcified iliac and femoral vessels, a silk woven catheter in the urethra as far as the prostate, the needle in place just below and behind the urethral bulb, and 3 cubic centimeters of sodium iodide injected. Fifty cubic centimeters of iodide were then easily injected under a pressure of 60 to 80 millimeters. The perineum now showed slight bulging, but the scrotum appeared to be the same size and preserved the rugosity of its skin. An x-ray film (Fig. 3b) at this stage revealed almost the entire perineum with exception of the root of

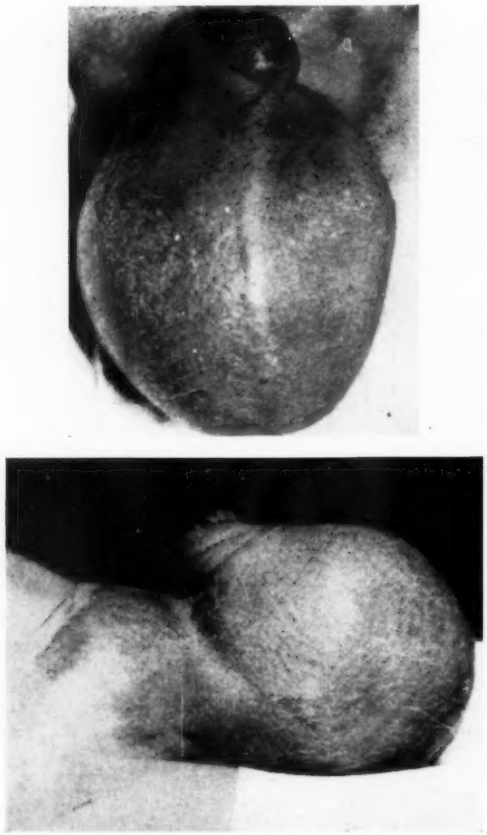

Fig. 7. Note marked resemblance between this clinical case of urinary extravasation and the result obtained in Figure 3 by injection. Both present symmetrical involvement of the perineum, scrotum, and groins without involvement of the penis.

the penis to be filled with the radio-opaque solution which was beginning to extend forward over the posterior and inferior aspect of the scrotum. After the injection of 150 cubic centimeters typical swelling of the perineum was noted with some distention of the posterior and inferior aspect of the scrotum which began to lose its rugosity. An x-ray film (Fig. 3c) at this stage showed complete filling of the perineum and slight, symmetrical, and complete filling of the scrotum. Two horns were now evident as projections on each side toward the inguinal regions, the right one being longer and more tapering. These projections represented infiltration along the spermatic funiculi. After injection of 250 and 350 cubic centimeters, the perineum remained swollen to the same extent as after 150 cubic centimeters, but the scrotal sac appeared progressively enlarged, more tense, and glossy with a loss of its rugosity. However, on physical appearance there was still no swelling of the penis or abdominal wall. X-ray films (Figs. 3d and 3e) made at these two stages revealed the persistently uniform distention of the perineum with the progressive enlargement of the scrotum and the two projections toward the groins.

None of the x-ray films in this series (Fig. 3) showed any involvement of the penis or the lower abdomen with the exception of the groins. Similarly, none of the films of this series showed any involvement of the vascular tree, which was a frequent and inadvertent accident in 4 of the 9 cases injected.

On dissection of the first case the blue fluid was easily traced from the confines of the superficial perineal pouch forward over the scrotal sac where it was found in the loose areolar tissue beneath the dartos. No blue was found in the deeper tissues of the scrotum nor in the tunica vaginalis testis. No blue was found in any of the layers of fascia of the penis, nor was there any blue within the corpus cavernosum or spongiosum. Blue was found extending around the loose areolar tissue surrounding both spermatic funiculi as high as the external inguinal rings, but no blue was found on the anterior abdominal wall, nor in any of the other fascial spaces in or about the bladder.

A glance at Figure 7 will show the marked resemblance between this clinical case of urinary extravasation and the result obtained in Figure 3 by injection. Both present symmetrical involvement of the perineum, scrotum, and groins without involvement of the penis. However, because the penis and lower abdominal wall are so frequently involved clinically, further attempts were made by the same technique. In the second case (Fig. 4), although the tissues were extensively infiltrated (patient had died with anasarca and marked scrotal edema), the injection fluid pursued the same course as in the first case; and none of it entered the penis or lower abdomen as demonstrated by inspection, dissection, and x-ray examination.

Of the 9 cases injected, the needle inadvertently entered the vascular tree in 4 cases. This modification of the results obtained is illustrated in the third (Fig. 5) and fourth (Fig. 6) cases. In these 2 cases x-ray films were made after injection of 3 cubic centimeters; and then after increments of 100 cubic centimeters. There was very little swelling of the perineum even after injection

a b c d

Fig. 8. a and b are views of a case of periurethral abscess, demonstrating the edema of the scrotum, root of the penis, and left groin due to the pressure of the mass in the perineum. c and d are illustrations of the same patient 1 week after incision and drainage were carried out revealing the disappearance of the edema when the pressure was released. (This is not the usual mechanism in urinary extravasation.)

of about 250 cubic centimeters and practically none in the scrotum until after about 350 cubic centimeters, because from the very beginning the iodide had entered the vascular tree, outlining the iliac vessels and all their tributaries. The perineum and scrotum were distended later, because the needle was withdrawn slightly after several hundred cubic centimeters had been injected. This demonstrates the ease with which the vascular system may be entered, although the fluid was always injected under light pressure. Even though the vessels and cavernous bodies of the penis were densely injected, this organ was not enlarged nor distended, since the tissues themselves were not infiltrated.

EVALUATION

Cystometrically, the normal expulsive pressure on voiding has been found to be between 60 and 80 millimeters of mercury. With irritative lesions a hypertonic bladder is characteristic and the pressure on voiding still higher. The pressure required in most of the injection experiments was also between 60 and 80 millimeters, so that the hydrostatic theory for infiltration of superficial perineal pouch and scrotum seems confirmed.

It is interesting to note that in none of the cadavers injected was any swelling of the penis or lower abdomen demonstrated by inspection, palpation, roentgenogram, or dissection. Even when the vascular tree had been entered, the fluid was confined to the vessels and cavernous bodies. This discrepancy between the clinical appearance in some cases of extravasation and that obtained experimentally by primarily infiltrating Colles' pouch is important.

The ease with which the vessels were entered suggests several factors which are operative in the live subject: Another glance at Figures 1 and 2 reveals that all periurethral inflammations or lesions must first penetrate the very vascular bulb or part of the spongiosum to reach the superficial perineal pouch. In this passage from urethra to fascial space they invariably involve the vascular tree, thereby easily setting up a vascular thrombosis or thrombophlebitis. Anterograde or retrograde extension of this process is favored by the contractions of the bulbocavernosus and external sphincter muscles, which are brought into play with each act of voiding. This explains the paradox in which the condition of extravasation is aggravated in those patients who continue to void. Moreover, this concept of the pathogenesis explains the development of extravasation without stricture or obstruction, and also the urgent necessity for diversion of the urinary stream, irrespective of whether the patient is voiding well or not. These muscles must be put at absolute rest to prevent them from squeezing the thrombosed bulb, and thereby extending the process into the scrotal and penile vessels.

This latter process accounts for the high incidence of toxicity and jaundice, the rapid appearance of the swelling of the penis and scrotum, and the ultimate gangrene. Once extravasated urine, blood, or an abscess occupy the superficial perineal pouch, it is easy to see how the pressure of the mass in the confined space would produce vascular obstruction of the scrotal vessels without actual thrombosis. This mechanism is seen in many periurethral abscesses. When the abscess is incised, the edema disappears, because of the release of pressure (Fig. 8).

Since the subcutaneous tissues of the penis and abdomen are not involved in the cadaver (where purely a hydrostatic process is operative), it must be assumed that the difference in the living subject is due to the presence of an active circulation or of other factors. It is probable that the loss of tonicity of the scrotum allows of greater distention in the cadaver without allowing the fluid to infiltrate the penis or lower abdomen.

Lastly, but invariably, the invasion of the loose areolar tissues by organisms of variable virulence accounts for the clinical picture.

Therefore, seven factors play parts in determining the characteristics of extravasation: (1) anatomical distribution of fascial planes; (2) nature and location of urethral lesion; (3) hydrostatic pressure of extravasated fluid; (4) vascular obstruction induced by pressure of perineal abscess or extravasated fluid; (5) occurrence of vascular thrombosis or thrombophlebitis; (6) elasticity, tonicity, and contractility of the tissues and muscles; (7) nature of the invading organism.

SUMMARY

In summarizing the facts gleaned from our experimental, bacteriological, and clinical knowledge, the two opposing theories for the pathogenesis of extravasation may be now balanced and perhaps correlated. In this connection, I believe that the condition known as "idiopathic scrotal gangrene" is only another form of urinary extravasation or periurethral phlegmon. All the reports (5, 8, 19, 22) on this mysterious condition use only one criterion in differentiating it from periurethral phlegmon; namely, the absence of stricture or obvious urethral lesion. In the light of the present study, idiopathic scrotal gangrene is easily explained without stricture or obvious urethral lesion.

FACTORS FAVORING HYDROSTATIC THEORY

1. Anatomically, Colles' fascia allows a progressive infiltration of the perineum, scrotum, penis, groins, and abdominal wall.

2. Kidd found a 2 per cent urea content in the fluid obtained from infiltrated tissues at operation.

3. Injection experiments on the cadaver reveal that the clinical appearances can be simulated (with the exception of penile and abdominal involvement) by using pressures and amounts of fluid comparable to those which are expected on voiding.

4. Cystometrically, the normal expulsive pressure on voiding varies between 60 and 80 millimeters of mercury. With irritative lesions a hypertonic bladder and still higher pressures are characteristic.

5. Pressures required in injection experiments were between 60 and 80.

6. The incidence of stricture and urethral trauma as reported by most observers is high.

7. The incidence of anaerobes as reported by observers of both periurethral phlegmon and idiopathic scrotal gangrene is low.

8. The following explanation is advanced for the paradox that the worst cases encountered are in those patients who continue to void: (a) Attention is not directed to the necessity for diversion of the urinary stream because of the absence of retention. (b) If abscess, stricture, or rupture of the urethra produces complete retention, extravasation may not occur (and diversion is practiced early). (c) But when abscess, stricture, or rupture of the urethra does not completely shut off the urinary stream, extravasation may occur; and the increased hydrostatic pressure necessary to overcome the obstruction may force urine into the tissues at the site of the defect in the urethra.

9. Voiding "squeezes" more urine into the tissues.

FACTORS FAVORING THEORY OF BACTERIAL INVASION AND VASCULAR INVOLVEMENT

1. Wolfer has proved that the injection of sterile urine will not produce this process, so that in the final analysis all cases are due to infection.

2. Albarran and Cottet maintain that actual urinary infiltration does not exist, that periurethral phlegmon is due to bacterial invasion only, especially anaerobes, and that the fluid in the tissues resembling urine is an acute inflammatory exudate.

3. Eisendrath and Rolnick claim that "50 per cent of cases present no obstruction to passage of the sound, and no stricture is found, and apparently there is no loss in the continuity of the urethra; 25 per cent have intact urethras and 25 per cent present impermeable strictures."

4. As regards the low incidence of anaerobes, it can be pointed out that anaerobic cultures were not made routinely in any series.

5. The following explanation is offered for the paradox that the worst cases encountered are in those patients who continue to void: (a) The very vascular bulb surrounds that part of the urethra most frequently involved in stricture, abscess, or trauma. (b) All periurethral inflammations must first penetrate the bulb or corpus spongiosum to reach the superficial perineal pouch. (c) In this passage from urethra to fascial space, they almost invariably involve the vascular tree; thereby easily setting up vascular thrombosis or thrombophlebitis. (d) These latter developments account for the high incidence of toxicity and jaundice, the rapid and enormous swelling of the penis and scrotum, and the ultimate gangrene.

6. Voiding "squeezes" more toxic products into the circulation and propels the thrombotic or thrombophlebitic process along the scrotal and penile vessels.

CONCLUSIONS

1. A newer concept of the pathogenesis is based on vascular involvement.

2. This concept not only explains the varied clinical syndromes encountered, but also yields a basis for rational treatment.

3. Diversion of the urinary stream is essential even in the absence of urinary obstruction.

4. Injection experiments conducted by x-ray and dissection together with clinical and autopsy records (13) failed to reveal any case wherein the tunica vaginalis testis was involved. Therefore, the avoidance of the deeper structures of the scrotum and especially the tunica vaginalis testis is stressed as a prevention of unnecessary mutilation.

I wish to express my sincere appreciation for the kind co-operation extended to me by Dr. Solomon Weintraub, pathologist, and Dr. William Snow, roentgenologist, Harlem Hospital.

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NEW FACTORS OF CLINICAL SIGNIFICANCE IN THE STUDY OF HUMAN SPERMATOZOA

JOHN W. HUFFMAN, M.D., Chicago, Illinois

THE problem presented by a couple complaining of infertility is never adequately investigated until the husband's seminal fluid has been examined. In conjunction with efforts to relieve infertility in gynecological patients, seminal fluid specimens have been examined from the husbands of 58 infertile couples. It seems worth while to report the results of these observations and to point out certain interesting and heretofore not appreciated factors involved in studying human sperm.

It is my custom to instruct the husband in detail about the procedure to be followed in obtaining sperm. The material is collected at coitus in a fishskin condom; rubber condoms are avoided because of the well-known tendency for spermatozoa to be killed by the action of the rubber or by the powder used in preserving the condoms. If sex contact has been indulged in with great frequency, several days' continence are advisable prior to obtaining a specimen. The material is kept at body temperature and is observed in the laboratory within 1 hour of ejaculation. The gross appearance of the sperm and its amount are recorded. Microscopic study of the fresh fluid at this time gives a rough estimate of the motility and the number of spermatozoa but is unsatisfactory for estimating abnormal forms unless they are present in large numbers.

From the Department of Obstetrics and Gynecology, Northwestern University Medical School and the Gynecological Service of Passavant Memorial Hospital, Chicago, Illinois.

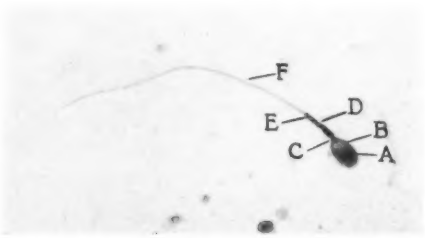


Fig. 1. Unretouched photomicrograph of a normal spermatozoon. The nuclear head is covered by, *A*, the acrosome and, *B*, the postnuclear cap. The neck, *C*, is between the nuclear head and the middle piece or body, *D*. At posterior end of middle piece is the shrunken ring centriole, *E*, beyond which is the flagellum or tail, *F*. ×700.

A spermatozoal count should be computed of every sample of seminal fluid, and a morphological study should be made of at least one specimen from almost every patient. There is a common feeling that the number of spermatozoa and their morphology is of no great significance provided there are "sufficient motile spermatozoa" in the fresh drop. This attitude is unfortunate because sperm counts and spermatozoal morphology can be rechecked quantitatively with a considerable degree of accuracy and give us our best gauge for estimating improvement and for comparison with earlier studies. The count may be made by using a white blood cell pipette and the usual Neubauer hemocytometer. The specimen should stand in the laboratory for 30 minutes or longer before diluting, in order to reduce the viscosity. The material is then thoroughly mixed and a 1:20 dilution is made, as for a leucocyte count. I have used a freshly prepared 0.5 per cent azochloramide solution in water as a diluting fluid; this gives a more even suspension than sodium bicarbonate and phenol diluents. It is essential that agitation of the pipette be gentle to insure against fragmentation of the spermatozoa and continued long enough to assure an even mixture. After the diluted material is placed in the counting chamber, 5 minutes should be allotted for settling before the count is begun. The enumeration is made by ascertaining the number of spermatozoa in 80 of the smallest squares of the chamber, as for an erythrocyte count. To the total thus obtained six ciphers are added to compute number of spermatozoa in 1 cubic centimeter of seminal fluid.

When the count is completed, the remainder of the fluid in the pipette is smeared upon clean slides, as in preparation of a thin blood smear. If there has been a notable deficiency in the number of spermatozoa, a second series of smears is made with varying dilutions of sperm and diluent so that one slide may be obtained with a sufficient number of properly distributed spermatozoa for a satisfactory study. These smears are fixed and stained by one of several methods, depending on the purpose for which they are to be used.

Most of the more rapid methods of staining used for bacteria are unsatisfactory for spermatozoa. Alum hematoxylin and eosin gives excellent results for routine study and counting and is not too laborious a procedure. In order to

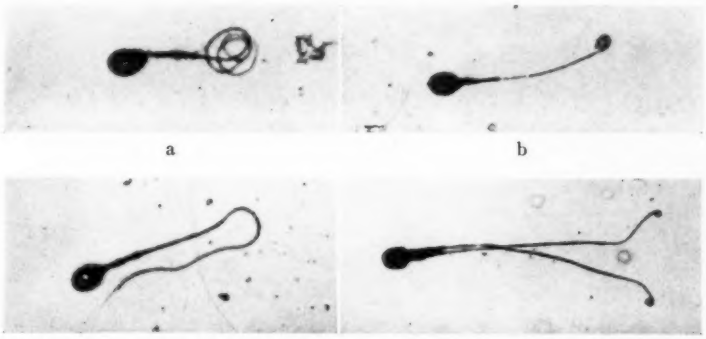


Fig. 2. Commonly observed types of spermatozoal abnormalities. a, Loosely coiled flagellum and abaxial implantation of the middle piece on the nuclear head, two minor defects; b, tightly coiled terminal flagellum, presumably an artifact; c, vacuolated nuclear head, a minor defect; d, thickened anterior centriole area and double flagellum, two major defects. ×885.

obtain satisfactory spermatozoal staining, it is necessary to modify the usual alum hematoxylin and eosin staining procedures for tissues as follows: (1) Dry the sperm smear in air and fix with gentle heat; (2) immerse in alum hematoxylin for 30 minutes (staining heads dark blue); (3) wash in tap water; (4) rinse in distilled water; (5) immerse in 70 per cent alcohol for 3 minutes; (6) immerse in eosin for 30 minutes (staining flagellum red); (7) rinse in 95 per cent alcohol; (8) rinse in water; (9) immerse in 95 per cent alcohol for a second time; (10) rinse in water; (11) immerse in absolute alcohol for 5 minutes; (12) clear in carboxyl xylol for 1 minute; (13) clear in xylol for 24 hours; (14) mount. When photomicrographs are to be made, this procedure is unsatisfactory, and one may resort to fixation with osmic acid and staining with Heidenhain's iron hematoxylin, using standard technique.

Two hundred or more spermatozoa in the stained preparation are examined under oil immersion and abnormalities of the nuclear head, neck, middle piece or body and flagellum are recorded. The appearance of a normal mature spermatozoon as seen microscopically is well known. It consists of a sleek, smooth, snake-like "head" to which is attached a long slender tapering tail. In stained preparations the "head" appears to consist of a large anterior and a small posterior portion, due to the presence of two thin cytoplasmic caps. The tail is divided into a thick anterior middle piece (the "body") and a thin

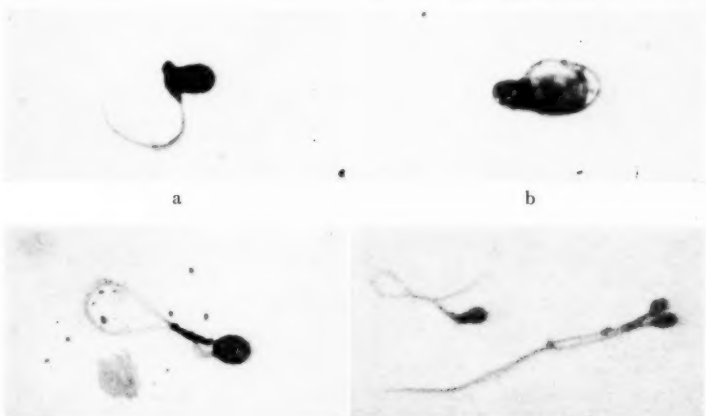


Fig. 3. Four major spermatozoal defects: a, Macrocephalic spermatozoon with gross deformity of the neck and anterior centriole area; b, tightly coiled flagellum with protoplasmic veil still attached to nuclear head; c, broken neck; d, doubled head and doubled middle piece with a single flagellum. ×885.

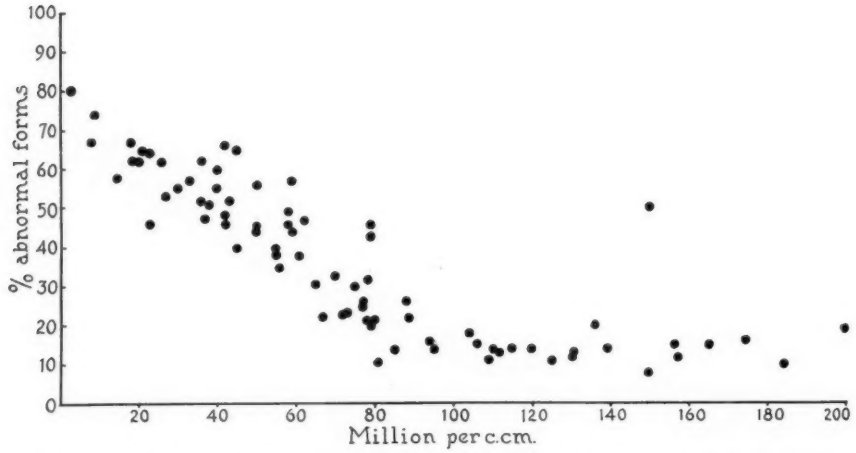


Fig. 4. Graph illustrating the relationship between the spermatozoal count and the percentage of abnormal spermatozoa in the stained smear. The abscissa represents the number of million spermatozoa per cubic centimeter, the ordinate the percentage of abnormal forms observed in the stained smears. Each point on the chart co-ordinates these findings in one specimen studied. It will be noted that the percentage of abnormal spermatozoa increases as the sperm count becomes lower.

posterior flagellum, the latter making up four-fifths of this portion of the spermatozoon. A short end piece or fine filament is sometimes to be seen at the tip of the flagellum.

The intracellular structure of a spermatozoon can rarely be seen. Gatenby and Beams, in their excellently illustrated contribution have given a more comprehensive understanding of the normal morphology than was heretofore available. They state that the mature spermatozoal "head" consists of a nucleus completely covered by two caps, the acrosome in front and the postnuclear cap behind. A vacuole (Fig. 2, c), the contents and function of which are unknown, is frequently observed within the nucleus. Posterior to the head is a constricted "neck." In reality this "neck" consists of the anterior head centriole and the neck proper, which is the space between the nuclear head and the top of the middle piece. The latter, commonly called the "body" (a misnomer which should be abandoned as a structure of that name goes to make up the postnuclear cap during spermatogenesis) is, according to Gatenby and Beams, formed of a single tube upon which the mitochrondria are situated. Its principal function is presumed to be concerned with propulsion of the organism. At the caudal end of the middle piece is the shrunken ring centriole, beyond which is the flagellum (or "tail").

Abnormalities in structure of human spermatozoa are of many kinds. They vary from major

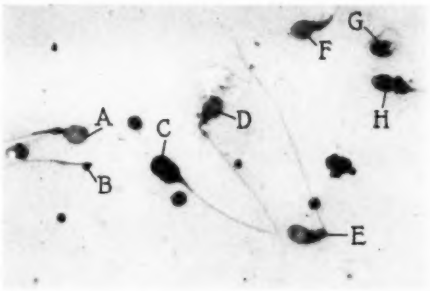
CLASSIFICATION OF ABNORMAL SPERMATOZOA

Abnormalities of the nuclear head
- Microcephalic, or little head, in comparison with other organisms in the specimen being studied
- Macrocephalic, or large head, in comparison with other organisms in the specimen being studied
- Double head
- Acephalic, or absence of the nuclear head
- Irregularity of the head outline (nicks, protoplasmic extrusions, etc.)
- Rough acrosome surface (so called penetrating membrane roughness)
- Solid staining and nonstaining heads
- Vacuolated nucleus
- Nuclear head still in cytoplasmic film or veil

Abnormalities of the neck
- Folded or acutely bent neck
- Broken or separated neck
- Abaxial implantation of the neck on the head
- Swollen neck
- Irregularity of the anterior centriole area, usually larger than normal

Abnormalities of the middle piece
- Broken or separated middle piece
- Thickened middle piece
- Irregularity of the middle piece outline
- Folded middle piece
- Spiral middle piece
- Abnormalities of staining of the middle piece

Abnormalities of the flagellum
- Absence of the flagellum
- Abaxial implantation of the flagellum on the middle piece
- Double flagellum
- Short flagellum
- Folded or acutely bent (does not include gently curling) flagellum
- Flagellum tightly coiled about the nuclear head



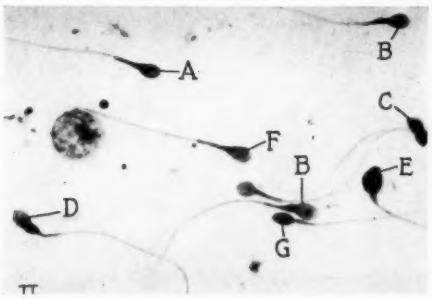


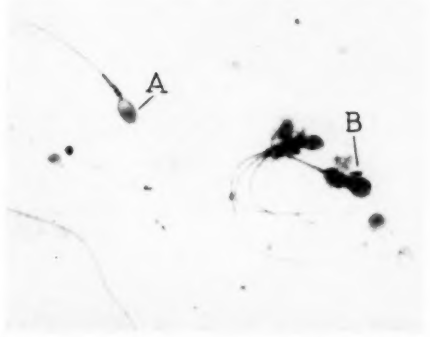
Fig. 5. Two groups of spermatozoa illustrating various types commonly seen in the stained smear. a, left, *A*, abaxial implantation of the middle piece on the nuclear head with enlargement of the anterior centriole area; *B*, microcephalic spermatozoon; *C*, macrocephaly; *D*, bent middle piece; *E*, enlargement of the anterior centriole area with abaxial implantation of the flagellum; *F*, swelling of the anterior centriole area; *G*, sharply curled flagellum; *H*, marked enlargement of the anterior centriole area. b, right, *A*, vacuolated spermatozoon; *B*, abaxial insertion of the middle piece on the nuclear head and swelling of the middle piece; *C*, double nuclear head; *D*, thickened anterior centriole area; *E*, irregularity of the nuclear head outline; *F*, normal spermatozoon; *G*, vacuolated nucleus. ×885.

self-evident deformities, such as absence of the nuclear head, to lesser defects, such as abaxial insertion of the tail into the middle piece; the latter, also lesser deviations from the normal, may or may not affect the ability of the spermatozoon to fertilize the ovum. In making these studies a modification of Moench's work has been found to be simpler and more practical.

The experience of many investigators indicates that the average number of spermatozoa per cubic centimeter of sperm is 100,000,000 and that a count of less than 60,000,000 is strongly suggestive of definite lowering of masculine fertility. It has also been a commonly accepted fact that abnormal forms should not exceed 15 or 20 per cent of the total number of spermatozoa in normal sperm.

In this study material has been examined from the husbands of 58 women who came because of their inability to achieve a pregnancy. Seventy-eight different specimens have been observed. The counts ranged from aspermia to 200,000,000 per cubic centimeter of seminal fluid and morphological abnormalities from 10 to 70 per cent in sperm containing sufficient spermatozoa to count.

A graphic record has been kept of the sperm counts and the percentage of abnormal forms in the material examined. On analysis of this graph a striking correlation between the number of spermatozoa per cubic centimeter and the percentage of abnormal forms was noted. Reference to Figure 4 will show that as the sperm count becomes lower the percentage of abnormal spermatozoa increases. In specimens containing over



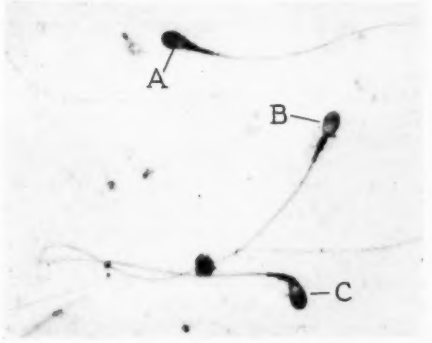


Fig. 6. Two groups of spermatozoa showing in the photomicrograph at left at *A*, a normal form, at *B* an hourglass shaped nuclear head with marked enlargement of the anterior centriole area and deformity of the middle piece. In the photomicrograph at right *A* and *B* are normal spermatozoa while *C* demonstrates the not uncommonly observed acute bending of the neck in an otherwise normal organism. ×885.

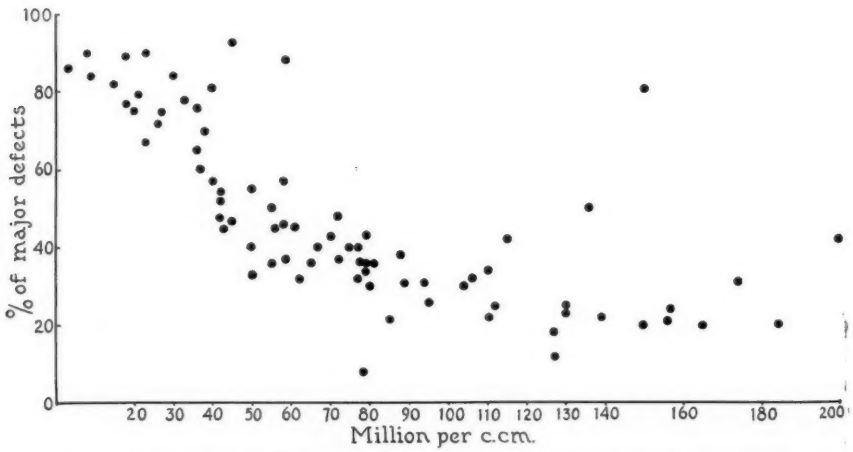


Fig. 7. Graph demonstrating the relationship between the percentage of the abnormal forms which belong to the "major defect" group and the sperm count. The abscissa represents the number of million spermatozoa per cubic centimeter, the ordinate the percentage of abnormal spermatozoa belonging to the "major defect" group observed in the stained smear. Each point of the graph co-ordinates these findings in one specimen. As count becomes lower, percentage of "major defect" forms becomes higher.

100,000,000 spermatozoa per cubic centimeter it is noted that the defective types constitute definitely less than 20 per cent of the total number of spermatozoa, in contradistinction to specimens below 100,000,000 per cubic centimeter, in which as the counts decrease the abnormal forms become more frequent. In other words, in a specimen containing 100,000,000 spermatozoa per cubic centimeter of which 15 per cent are abnormal, approximately 85,000,000 normal organisms will be available for fertilizing purposes; whereas, in a specimen containing 30,000,000 spermatozoa per cubic centimeter with 60 per cent abnormal forms only 12,000,000 morphologically normal spermatozoa per cubic centimeter can be considered functionally active. As the counts continue to decrease, there is a correspondingly greater discrepancy between apparent and real potency of the specimens.

The relative importance of various abnormalities of spermatozoal structure in decreasing human fertility remains a matter for conjecture. More than forty different abnormal forms have been described, most of which are included in the practical classification here described. Exceptions to this classification are a rarity. During the course of this investigation the types of deformities making up a preponderance of the defective spermatozoa observed in the stained smears were recorded and correlated with the sperm counts. While it is not justifiable to draw other than general conclusions from these correlations, the fact that some relation exists between the preponderant types of abnormality and the count is of great interest. It would appear logical to assume that defects of the nuclear "head" and of the neck with its anterior centriole would be more apt to interfere with proper fertilization of the ovum than would lesser peculiarities in the structure of the middle piece and the flagellum. Therefore, certain abnormalities which have been distinguished as "major defects" have been arbitrarily placed in a group in contradistinction to another group of "minor defects." In the first group have been placed those deformities which appear most likely to impair the life, the function, or the motility of the organism; among the minor defects are placed those peculiarities of structure which are questionable etiological factors in impairing the potency of the semen, either because no reason can be given as to why they should be detrimental to the spermatozoon or because it is suspected they may be artifacts. The two groups are:

MAJOR DEFECT GROUP

Macrocephalic abnormalities of the nuclear head
Microcephalic abnormalities of the nuclear head
Double nuclear head
Absence of the nuclear head
Broken or separated neck
Swollen neck region
Abnormalities of the anterior centriole area
Broken middle piece
Absent flagellum
Double flagellum
Flagellum tightly coiled about the nuclear head
Head still in cytoplasmic veil

MINOR DEFECT GROUP

Irregularity of nuclear head outline
Roughened acrosome surface
Abnormalities of staining
Vacuolated nucleus
Folded neck
Abaxial implantation of neck on head
Thickened middle piece
Irregularity of middle piece outline
Folded middle piece
Spiral middle piece
Abaxial implantation of flagellum on middle piece
Short flagellum
Folded flagellum

At the time the morphological studies were made the defective types observed were segregated into the two groups. The percentage of the major defect group in relation to the total number of defective spermatozoa seen on the stained slide was then determined. When this percentage was correlated with the sperm count, it was seen (Fig. 7) that as the sperm count decreases the percentage of abnormal forms belonging to the major defect group increases materially.

While it is realized that motility of the spermatozoa is of vital importance in estimating the potency of a specimen of seminal fluid, it has intentionally not been considered here. Estimation of motility constitutes a variable factor not subject to standardization. The time elapsing between ejaculation and examination, changes in temperature, and interpretation by the examiner of what he considers the approximate percentage of motile spermatozoa in the fresh drop make any statement as to motility a rough approximation rather than a quantitative report. A record of the approximate percentage of motile spermatozoa per high power field in the fresh drop of the specimens reported herewith was kept, but it was felt that the addition of this factor to the present study would not enhance its accuracy and would confuse the results. It is my impression that for the most part motility will not correlate as closely with the count as the morphological variations have done. Despite this, it is imperative that a careful attempt should be made to estimate motility at the time the warm material is examined. While the movement of the spermatozoa can not be measured quantitatively, it is of utmost importance that the examiner has an impression of the approximate percentage of active spermatozoa when he places a final value on the specimen. The individual examiner will, perforce, establish his own "standard" of normality, based on experience.

RÉSUMÉ

These observations are of interest because of the light they throw on genital function. It would appear that when the testes excrete spermatozoa in decreased numbers, their aggregate quality becomes definitely inferior. This factor, in so far as can be discovered, has hitherto not been appreciated in evaluating seminal specimens. This would seem to be a more valid reason for careful and repeated sperm studies in clinical practice than any previously suggested. While it is no doubt true that a man of mediocre fertility, when mated with a woman of marked fecundity, may beget a child, too often there are factors in both the husband and the wife which, in combination, are sufficient to prevent gestation. It behooves us, therefore, to arrive at as exact a knowledge of both partner's procreative powers as we are able. To do this, we must do more than hazard an opinion, arrived at by cursory examination, that there are "sufficient motile spermatozoa of normal type" in a specimen brought to us for study. The knowledge that the husband has a definite decrease in his potency will, perhaps, cause treatment to be directed toward improvement in his condition. The resultant increase in his fertility may thereafter compensate for those factors affecting his wife, and pregnancy will result.

While insufficient material has been examined to warrant any definite conclusions, the abnormalities observed, when compared with the illustrations prepared by Gatenby and Beams, strongly suggest that many of these abnormal forms are in reality immature spermatozoa rather than deformities of the mature spermatozoon.

CONCLUSIONS

As the number of spermatozoa per cubic centimeter of human seminal fluid decreases, the percentage of abnormal forms increases. Coincident with the increase in abnormal forms the types of abnormalities noted become more definitely those which would be expected to impair fertility. Semen which has a spermatozoal count definitely below normal, therefore, has a decreased potency, not only in quantity but also in quality. This observation lends added weight to the dictum that careful study of the seminal fluid is imperative in every case of human infertility. It is suggested that some of the abnormal forms of spermatozoa seen in human seminal fluid are in reality immature products of spermatogenesis.

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RECONSTRUCTION OF THE EAR

JULIUS NEWMAN, A.B., M.D., F.A.C.S., Newark, New Jersey

RECONSTRUCTION of the ear has long been the *bête noire* of the plastic surgeon. This pessimism has, perhaps, been justified by the difficulty of the procedure, the length of time needed, and the high cosmetic standards required. A reconstructed ear is satisfactory only if the patient can carry out his daily routine without feeling that the fabricated organ attracts public attention.

The surgically shaped ear must be of approximately the size, shape, and angle of the normal ear. The transplantation of an amorphous blob of skin and cartilage should not satisfy the surgeon. In the past, reconstructed ears have looked clumsy and bulky because an excessively thick tube pedicle was used for the helix. Certainly thinner tube pedicles can be made to function without loss in migration if the pedicle is delayed by undercutting and resuturing. Overzealous débridement in traumatized ears is often the prelude to an unsatisfying result. Every effort should be made to preserve the cartilage of the lacerated ear. Since in local injuries the skin will frequently retract, thus exposing the cartilage, this tissue should be thoroughly cleansed, resutured carefully, and a compressive dressing applied. Conservative treatment at this juncture saves much difficult surgery at a later date.

Fig. 1a.

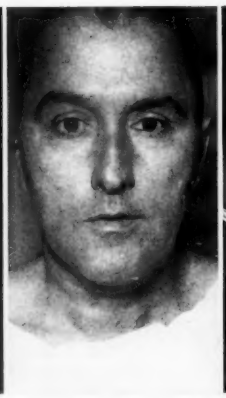


Fig. 1b.

Fig. 8.

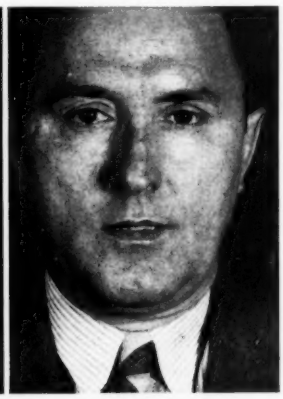


Fig. 9.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 7.

Ear reconstruction should not be attempted until the patient has attained full growth. Only at this period can proper measurements be taken from the full grown ear on the opposite side. Careful planning gives the opportunity to build an ear of about the size of its fellow.

The original flap, which goes to make up the fossa of the helix, is made in the mastoid region. This flap need not extend beyond the hairline, for if it does we are inviting the growth of hair on the ear. Nor can we evade this difficulty by the depilatory use of electrolysis or x-ray, for these procedures might jeopardize the cartilage graft.

In the 2 cases here reported, we were dealing with traumatic loss of the greater portion of the auricle following automobile accidents. Each operation was performed in 9 stages. Ether anesthesia was used during removal of the rib cartilage while local anesthesia was used during the remaining stages. In general, we followed closely the technique of George Warren Pierce. Supraclavicular skin in the form of a tube pedicle was taken for the helix. The pedicle was shifted every 3 weeks from its original site to the new auricle. Costal cartilage gave support to the new fossa of the helix. A Thiersch graft from the thigh supplied skin for the back of the mastoid flap and for the skin defect in the skull. Figures 1a and 1b show the deformed ear before operation; Figures 8 and 9 indicate the operative result.

TECHNIQUE

Stage 1. The normal (left) ear was measured accurately. The new ear was outlined to scale on the right side of the patient's skull; brilliant green was used as the drawing medium. We could thus visualize the dimensions of the fossa of the helix and the height and thickness of the new helix. A piece of rib cartilage was then removed from the right costochondral junction. This cartilage was cut down to proper size and inserted in the right mastoid area directly above the external auditory meatus (Fig. 2).

Stage 2. A tube pedicle was made in right supraclavicular region, measuring ½ by 5 inches. (Fig. 2).

Stage 3. A curved incision was made in the right mastoid region, partly surrounding the cartilage graft. The size of this cartilage-bearing graft was only slightly larger than the fossa of the helix of the normal ear. A Thiersch graft was cut from the thigh and wrapped around a dental stent mold (Fig. 3). The dental stent was then inserted under this flap, and the flap resutured.

Stage 4. The medial end of the pedicle was cut and attached to the region below the lobule of ear, as indicated in Figure 4.

Fig. 10.

Fig. 11.

Stage 5. The cartilage-bearing flap was elevated, its lower border trimmed. The remnant of the helix on the deformed ear was cut away, but not sacrificed. The cartilage-bearing flap was then attached to the remaining concha of the deformed ear (Fig. 5). The lateral end of the tube pedicle was detached and reattached to the area directly above the tragus.

Stage 6. The lateral end of the tube pedicle was detached and attached to an area near the tragus. The tube pedicle now crosses the ear, as shown in Figure 6.

Stage 7. The pedicle was put into final position, ready to drape the new fossa of the helix (Fig. 7). Throughout all these pedicle shifts we had no difficulty with color change, edema, blebs, or other untoward complications.

Stage 8. At this period the tube pedicle was opened along its suture line. The cartilage-bearing flap was denuded at its borders and the helix sewed into place (Fig. 8).

Stage 9. As a finishing touch, the various scars were removed and the necessary modeling performed (Fig. 9).

Figures 10 and 11 show the preoperative and postoperative photographs of another ear reconstructed by the same technique. The new helix is still paler than the rest of the ear. This, in time, assumes the same coloration.

The reconstructed ear in Case 1 is somewhat closer to the side of the head than the normal ear, as indicated in Figure 9. This could have been remedied easily enough, but the patient was satisfied with the result and preferred not to have any further surgery. The operations on these patients were usually scheduled for weekends to give the patients a minimum loss of employment time. They spent an aggregate of 18 days in the hospital, each losing only 12 days from work.

ONE STAGE OPERATION FOR CLOSURE OF LARGE DEFECTS OF LOWER LIP AND CHIN

HANS MAY, M.D., F.A.C.S., Philadelphia, Pennsylvania

THE defect left after radical excision of a malignant growth of the lower lip is usually so large that transplantation of flaps either from the immediate neighborhood or from some distant parts is needed for closure. The transplantation of a flap from the upper lip into the defect of the lower lip is a simple and effective method of closing small areas (Estlander, Buck, Brown, Padgett). Larger defects require other methods, a method which is based upon the excision of two triangular pieces of cheek from the nasolabial regions (Bernard, Burow, Martin). But defects from removal of more than two-thirds of the lower lip and chin cannot, as a rule, be closed satisfactorily by the latter method, particularly if the defect reaches beyond the corners of the mouth. The customary procedure to close such large defects consists of the transplantation of a flap from distant parts of the body. The lining and the lip itself are formed by skin grafting or transplanting local flaps. The disadvantages of this method are the considerable amount of time required for the procedure, the difference in skin color and texture and the loss of function. For certain defects, particularly those resulting from intensive radiation, such tube flap transplantations are the only means of closure. For primary repair, however, transplantation of local flaps can be employed with great success. The author wishes to call attention to an operation which, in his experience, is vastly superior to tube flap transplantation—an operation, as far as can be ascertained, not commonly known.

This method was originally devised by Dieffenbach, in 1834. Its principle is based upon the creation of a triangular defect which is closed by shifting two square flaps around one point of rotation from the immediate neighborhood into the defect. The two square flaps for closing the triangular defect of lip and chin in Dieffenbach's original operation reached from the corner of the mouth to the anterior border of the masseter muscles (including a small mucous membrane flap for the formation of the new lip) and from here down to the mandible. The flaps consisted of the entire thickness of the cheek. These were shifted into the defect. The two secondary defects in front of the masseter muscles could be closed only partly and the rest was left to granulate. Remarkable as Dieffenbach's plan was, the creation of two secondary defects through the entire thickness of the cheeks, has disadvantages. It was improved by Adelmann, of Dorpat, and Szymanowski, of Kiev, in 1858. The former advised cutting broader skin flaps and in this way closing the secondary defects, at least from the outside, while the latter improved the method by leading the upper incisions not horizontally, but obliquely upward to facilitate closure of the secondary skin defects. But as far as can be ascertained no effort has been made as yet to close the muscle and mucous membrane defects in front of the masseter muscle. This triangular defect in the midst of the cheek covered only by skin is not only a source of infection but also the cause of a depression of that area. I overcame these disadvantages by transplanting a flap of the masseter muscle into the defect, as I shall describe in more detail.

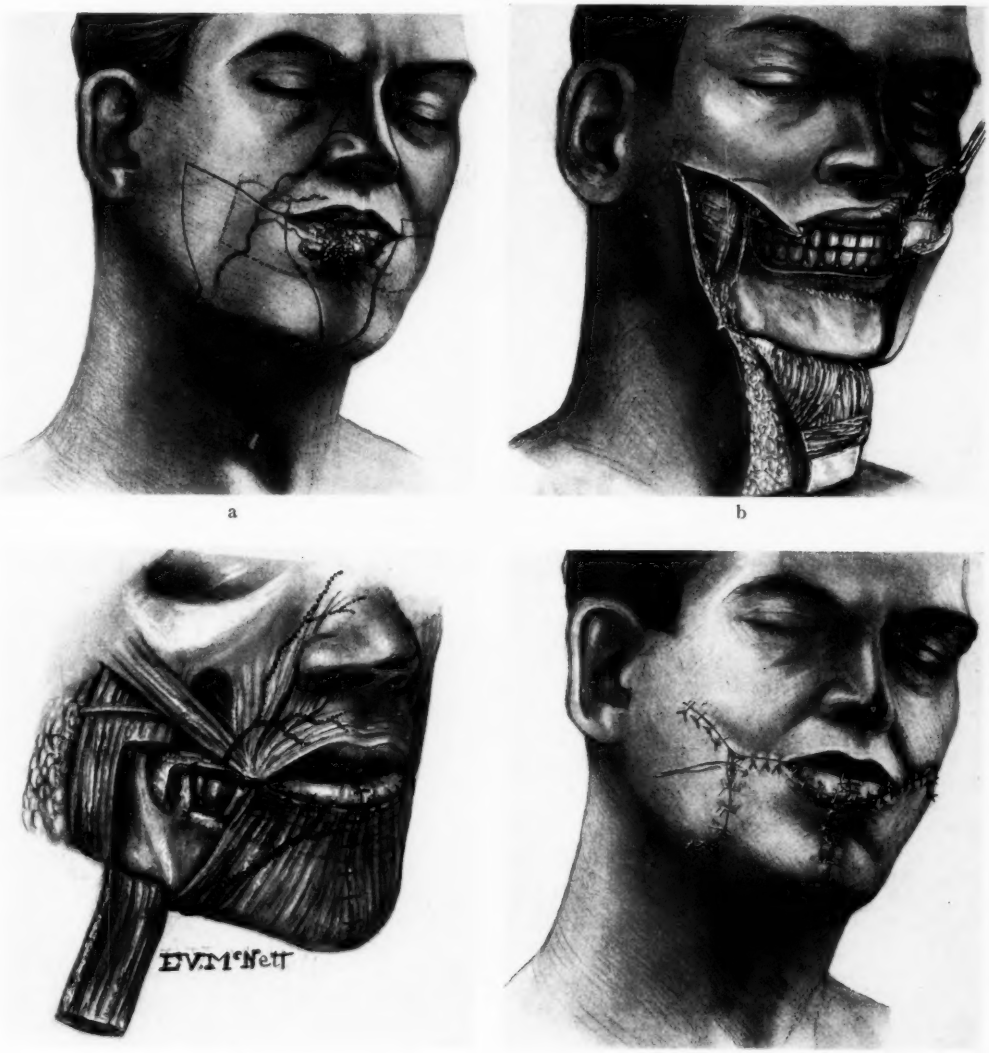
From the Lankenau Hospital, service of Dr. George P. Muller.

TECHNIQUE

The operation is carried out as follows:

The patient is operated upon under general anesthesia. The incisions are outlined with one of the aniline dyes. Before the anesthetic is administered I let the patient contract his masseter muscle and mark its anterior border at its upper and lower insertion with a drop of methylene blue injected percutaneously. Before operation I also mark the orifice of Stenson's duct.

Excision of lip and chin. The tumor, together with the soft parts of the entire chin, is excised in a heart shaped rather than a wedge shaped piece (Dieffenbach). This results later in a more normal looking profile with a dimple in the center of the chin. The patient in Figure 2d had a heart shaped excision; the patient in Figure 3a, a straight wedge shaped. If it is possible the excision should not include the entire corners of the mouth. The reconstruction of a corner of the mouth involves another problem. In those cases I leave a very small flap of the lower lip at either side of the mouth as outlined in Figure 1. The incisions on either side meet each other at a point below the



a b c d

Fig. 1. a, Large cancer of lower lip; heart shaped excision of lower lip and chin is outlined, also the two square flaps which are to cover the defect; two small flaps at corners of mouth are preserved; the inside incisions for mobilization of the flaps from the mandible and from the anterior border of the masseter muscles are outlined by dotted lines, also the small mucous membrane flaps for formation of the vermilion border. b, The right flap is mobilized; the small mucous membrane flap is sutured to the outer edges of the main flap; the left mucous membrane flap for formation of the vermilion border is being freed. c, Closure of the triangular muscle and mucous membrane defect in front of the masseter muscle by mobilization of the mucous membrane as far as possible and transplantation of a flap consisting of the lower anterior half of the masseter muscle. The mobilization of the flap is exaggerated in this drawing for demonstration purposes. d, The original and secondary defects are closed.

center part of the mandible. This point becomes the point of rotation around which two square flaps are turned from the immediate neighborhood (Fig. 1).

a b c d

Fig. 2. a, Patient with a large squamous cell carcinoma of lower lip; no evidence of metastasis. Line of excision outlined. b, Same patient 5 days after operation. c and d, Same patient 13 months after operation.

Outlines of the flaps and formation of the new lip. For the formation of the right flap—likewise the left—the following incisions are made (Fig. 1). From the right corner of the mouth an incision is carried obliquely upward to about 1½ inch in front of the tragus of the ear. From there the incision is carried downward at an angle less than a right angle ending below the mandible. The next step is the formation of the right half of the future lower lip. From the corner of the mouth to the anterior border of the masseter muscle the incision includes skin and muscles while the mucous membrane is dissected free from the upper wound edge for about 1 centimeter. By doing this the external maxillary artery is encountered and ligated. The facial vein is found posterior and more superficial to it. It is also ligated and separated. Still more posterior and above is Stenson's duct; care must be taken not to injure it. The mucous membrane is now separated 1 centimeter above the main flap. This tiny mucous membrane flap is now turned outward to form the right half of the future lower lip (Fig. 1b). The lateral third of this new lip, due to thickness of the subcutaneous and muscle tissue, is broader than the median parts, which results in protrusion instead of gradual disappearance of the lateral part of the vermilion border. In the first case, I had to perform a secondary corrective operation; thereafter I avoided it by excising some of the subcutaneous and muscle tissue of the lateral third of the new lip and trimming the mucous membrane accordingly. Martin also recommends this for Bernard's operation.

Fig. 3a Fig. 3b

Fig. 3. a, This patient had a squamous cell carcinoma of lower lip which was excised but recurred; radiation could not control the growth either; therefore a radical excision was performed with resection of central part of mandible; the defect was covered with a bilateral flap according to Figure 1, a to d. Bone transplantation was carried out subsequently. Patient 1 year after operation. b, Same patient 1½ years after operation.

Fig. 4a Fig. 4b

Fig. 4. a, Patient, aged 74 years, had a small squamous cell cancer in left half of lower lip which had been unsuccessfully treated by radiation; therefore the left half of the lower lip was excised. The defect was covered with a flap rotated from the left nasolabial region. The histological examination, however, showed numerous cancer cells at the edges of the excised part, at least one-half inch away from the ulcer. Therefore a more radical operation had to be performed. The patient, in this figure, is shown 10 days after the first operation. The heart shaped excision is marked out; notice that one-fifth of the right lower lip was left intact, that the left side of the excision included considerable parts of the cheek; the defect was covered with a unilateral composite flap from the left side and rotation of the right cheek after triangular shaped excision of the right nasolabial region with lengthening of the lip (Burow). b, Same patient 10 months after the operation had been carried out.

Mobilization of the flap. The entire flap is now mobilized (Fig. 1b). Its lateral half is mobilized by outside incisions consisting of skin only. Its median half is mobilized by inside incisions, comprising the entire thickness of the cheek. The incisions for the lateral half penetrate not deeper than to the fascia parotideo-masseterica, from which the lateral half of the flap is separated. The incisions for the median half begin with separation of the mucous membrane along its reflection at the mandible and reach from the defect to the anterior border of the masseter muscle. This incision includes the mucous membrane only. The other inside incision leading vertically upward connects this latter point with the outer edge of the newly formed lip. This incision penetrates through mucous membrane and the muscles. The entire flap is now turned downward and by blunt dissection separated from the mandible until the submandibular spaces are exposed, an important step, since the flap will not be flexible enough unless it is separated entirely from the mandible.

Closure of defects. Both flaps, which have surprising mobility, are shifted toward the midline into the defect. By doing this a secondary mucous membrane and muscle defect is created in front of the masseter muscle, also a secondary skin defect where the lateral half of the flap was taken. To close the muscle and mucous membrane defect I advise the following procedure: a flap of the masseter muscle consisting of its anterior lower half is separated from the underlying buccinator muscle and shifted anteriorally into the muscle defect (Fig. 1c). The closure of all defects is now carried out in the following order: connection of the lateral edge of the new lip with the corner of the mouth; connection of the mucous membrane of the flap with the gums; closure of the posterior mucous membrane defect as far as possible by mobilization of the posterior mucous membrane lip; connection of both flaps to each other in a three layer suture; connection of the masseter flap to fill the defect; connection of the lateral half of the main flap with the skin edges; closure of the secondary skin defect by starting with closure of the lateral corner. This is easily accomplished since the outer angle has been made smaller than a right angle (Szymanowski) (Fig. 1d). A drain is inserted in the lateral lower wound angle. The patient is fed through a Jutte tube.

If the tumor has involved the mandible the mandible can be resected at the same sitting after proper pre operative splinting. Dissection of glands, however, should be done in a second stage.

The same operation can be performed unilaterally for unilateral lesions; it is particularly of value for closure of those unilateral defects whose lateral borders reach beyond the corner of the mouth (Fig. 4). If transplantation of such a unilateral flap is not enough to close the defect, it may be combined with the method of either Burow or Estlander at the other side (Fig. 4).

ADVANTAGES OF OPERATION

I have employed the described operation on 4 patients with extensive carcinomas of lower lip and chin. In 3 instances a bilateral flap transplantation was performed, in one instance a unilateral, combined with Burow's method at the other side. In 1 case a resection of the central part of the mandible had to be added followed by bone transplantation later. In 2 cases the regional lymph glands were subsequently dissected. The youngest patient was 34 years of age, the oldest 74. The last operation (the 74 year old patient) was performed under sodium pentothal oxygen anesthesia. The anesthesia was injected through a vein of the ankle. Thus neither the anesthetist nor the operator were in each other's way. This patient was discharged on the seventh day after operation. None of the other patients were hospitalized longer than 11 days after the operation. Primary healing resulted in all cases. In addition to the short time of hospitalization, other advantages of this operation contrasted with the tube flap transplantation are: excision of tumor and closure of defect in one sitting, replacement of lost structures by identical structures, thus restoring original function and appearance.

With this operation available there should be less tendency to carry the incision too close to the tumor when a more radical excision seems necessary to lessen any possibility of recurrences.

SUMMARY

A one stage operation for closure of large defects of lower lip and chin is described. The principle involved in this operation is based upon the creation of a triangular defect which is closed by shifting one or two square composite flaps from the immediate neighborhood into the defect around one point of rotation.

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RESECTION OF DUODENUM AND HEAD OF PANCREAS FOR CARCINOMA OF THE AMPULLA

THOMAS G. ORR, M.D., F.A.C.S., Kansas City, Kansas

IN 1935 Whipple, Parsons, and Mullins (14) reported successful resection of the duodenum and a portion of the pancreas for carcinoma involving the ampulla of Vater and head of the pancreas. Since that date 14 cases have been mentioned in the literature which have been treated by the technique described by these authors with only slight modifications. The following case is recorded as an additional example of this method of treatment:

C. C. T., Hospital No. 86,563, male, aged 47 years, was admitted to the University of Kansas Hospitals, April 24, 1940. The gall bladder and appendix were removed in 1934 followed by disruption of the abdominal wound which required 42 days to heal. Since then he has had what he calls attacks with his stomach with some epigastric distress and discomfort in the region of the right scapula. On December 26, 1939, his stomach trouble increased and he had some vomiting, his skin became yellow, and the stools were light in color. He lost 30 pounds in weight in 4 months and now weighs 128 pounds.

Examination showed that he was undernourished and jaundiced. The blood pressure was 95 systolic and 65 diastolic. There was an incisional hernia in the right upper quadrant and a slightly tender liver was felt 3 centimeters below the costal margin. A mass was not felt. There was a small right inguinal hernia. Urinalysis showed a faint trace of albumin and bile. The hippuric acid liver function test was normal. The hemoglobin was 84 per cent, red blood cells 4,280,000, and white cells 8,650. The prothrombin time was 13.1 seconds, clotting time 7½ minutes, and bleeding time, 2 minutes. The Wassermann and Kahn tests were negative. The icterus index was 25. The blood chemistry was essentially normal with the exception of a slight decrease in the total blood cholesterol and a decrease in the percentage of cholesterol esters. The kidney function test was normal. X-ray examination was negative except for moderate dilatation of the duodenum and delayed emptying in the second portion. After 6 hours there was a slight retention of barium in the stomach.

The first stage of operation was done on April 20, 1940. The biliary tract was explored through an upper right paramedian incision. Many adhesions were encountered making exposure of the common duct very difficult. The gall bladder had been removed and the common duct was dilated, measuring 2.5 centimeters in diameter. At the ampulla there was a small firm mass about 1 centimeter in diameter, the nature of which could not be determined by palpation. The duodenum was opened and a tumor was found involving the ampulla, which was considered carcinoma. The duodenum was closed and an anastomosis was made between the common duct and the antrum of the stomach by means of a transverse incision 2 centimeters long in the duct (Fig. 1). Catgut was used for the mucosal and fine silk for the serosal sutures. A posterior gastroenterostomy was then done, and the old incisional hernia was repaired. The patient made an uncomplicated recovery from this operation.

The second stage was carried out on May 15, 1940. Through an epigastric transverse incision, the common bile duct was ligated and sectioned, and the duodenum and a wedge-shaped section of the head of the pancreas were removed. The duodenum was divided at its junction with the pylorus and through its third portion. Closure of the proximal and distal ends was made with two rows of sutures. The common duct was doubly ligated and divided about 2 centimeters above the ampulla. The V-shaped wound in the pancreas was closed with interrupted sutures of silk (Fig. 1). Two small Penrose drains were placed down to the duodenal bed. The wound was closed with interrupted sutures of silk.

Gross and microscopic pathology. "The duodenum measured 7 centimeters in circumference and the specimen together with the pancreas weighed 45 grams. The external surface of the duodenum was somewhat hemorrhagic and showed a number of fibrous adhesive tags together with an adherent portion of pancreas which measures 4.5 by 4 by 1.5 centimeters. The wall of the duodenum did not appear thickened. The mucosa was light gray in color and was covered by a small amount of mucoid material. The ampulla of Vater was quite prominent. There was an elevation beneath the mucous coat which measured 25 by 12 by 8 millimeters. A probe could be readily passed from the mouth of the ampulla into a portion of the common bile duct. The bile duct appeared dilated and measured 12 millimeters in greatest diameter. The tissue around the opening of the ampulla of Vater was light gray in color, firm, and rubbery in consistency and on cut section had a somewhat cellular appearance. The attached portion of pancreas was firm and rubbery in consistency and showed distinct lobulation."

Microscopic examination showed "acute and chronic catarrhal duodenitis; chronic ulcerative choledochitis; adenocarcinoma of the ampulla of Vater; chronic pancreatitis."

Following the operation there was a profuse drainage of clear fluid from the wound which in a few days caused definite excoriation of the surrounding skin, which was quite painful. Following the operation in 3 days the icterus index rose to 50 and on the eighth postoperative day had dropped to 15. On the second day following the second stage operation the blood amylase was 202 milligrams which dropped to 108 milligrams on the third day. Drainage from the wound was strongly positive for pancreatic ferment. Five days after the second stage the blood amylase was 75 milligrams. This gradually decreased until at the end of 20 days the amylase was 31 milligrams. At that time the icterus index had dropped to 6. At the time of discharge June 15, 1940, 31 days following the second stage operation, the wound was almost healed with only slight drainage.

He returned to the Hospital on June 28, 1940, 44 days after the operation, complaining of chills, fever, nausea, and vomiting. After admission to the hospital he did not

From The University of Kansas Hospitals.
Presented before the Western Surgical Association in Topeka., December, 6, 1940.

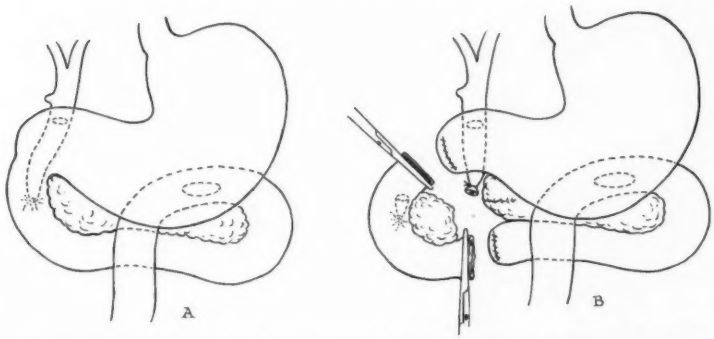

Fig. 1. a, First stage. Choledochogastrostomy and gastrojejunostomy. b, Second stage. Ligation and section of common bile duct; resection of duodenum and head of the pancreas.

have any further chills or fever and recovered from what apparently was a mild cholangitis. The icterus index was 8. In 5 days he was dismissed.

He was readmitted to the hospital a third time on August 26, 1940, complaining of pain, weakness, drainage from the wound, indigestion, and loose foul smelling stools. On July 8, 1940, he began to have colic-like pains in the epigastrium associated with clear drainage from an opening at the lower end of the scar. Drainage was profuse for several days. The opening closed spontaneously on July 14, 1940, and began draining again on July 17, 1940, and again later closed. On August 4, 1940, the fistula again opened and drained 14 days. It then closed and remained closed until after the third admission to the hospital, August 26, 1940. Two days after admission there developed a profuse flow of clear irritating fluid which was positive for amylase. There was a small mass beneath the vertical scar which was quite tender. This mass beneath the scar increased in size until it was obvious that an abscess had developed and drainage was necessary. On September 13, 1940, the abdominal wall abscess was opened and drained and the pancreatic fistula was explored. The fistulous tract led into a cavity measuring approximately 6 by 8 by 10 centimeters, extending down to the pancreas. It was completely packed with gauze and a cigarette drain was passed down beside the gauze.

When the pack was removed at the end of a week a small fistula developed from the lower ileum. Since then there has been an intermittent discharge of pancreatic juice and bowel content.

The patient lost 25 pounds following the operation which has been regained. He had occasional epigastric cramps and is very uncomfortable at times from the irritating effect of the pancreatic juice on the skin.

TECHNIQUE OF OPERATION

It is the general opinion at present that the operation should be done in two stages. At the first stage, as described by Whipple, Parsons, and Mullins, the gall bladder is anastomosed to the stomach, the common duct is ligated and sectioned, and a posterior gastroenterostomy is done. To minimize ascending gall duct infection Whipple (13) has more recently recommended section of the jejunum, cholecystjejunostomy, end to side jejunojunostomy, ligation and section of the common duct, and gastroenterostomy.

At the second stage the duodenum is sectioned at or near the pylorus and through the third portion and a V-shaped resection of the head of the pancreas is done. The proximal and distal ends of the divided duodenum are closed. The duodenal bed is drained.

COMPLICATIONS OF THE OPERATION

Since this operation is still on trial a review of the complications encountered by various authors may be of value. The reported cases are listed in Table I.

The first case of Whipple, Parsons, and Mullins developed a duodenal obstruction at the site of a duodenoduodenostomy following resection of a portion of the duodenum with the head of the pancreas. This necessitated a third operation. A gastroenterostomy and enteroenterostomy were done. After freedom from symptoms for 7 months this patient developed abdominal pain, vomiting, chills and fever and died 8 months after operation as a result of contraction of the cholecystgastrostomy opening, liver infection, and septicemia. The second case of these authors had some discharge of pancreatic juice evident on the third postoperative day. This decreased after the eighth day, but there was still present some drainage when the patient was discharged on the eighteenth day. About 2 months after the operation sudden epigastric pain developed with vomiting, abdominal tenderness and leucocytosis. The abdomen was explored and a small pocket containing 20 to 30 cubic centimeters of yellowish fluid was found in the right upper quadrant which showed a culture of Bacillus coli and nonhemolytic streptococcus. The area was drained and

the patient recovered. Pancreatic juice drained from the wound for 2 weeks. This patient died 32 months after operation, with liver metastases.

Orator's patient drained pancreatic juice amounting to 300 to 500 cubic centimeters daily. On the thirteenth postoperative day nausea and vomiting developed, followed the next day by a discharge of bile from the drainage opening. On the fifteenth postoperative day the bile duct ligatures and an ascaris were found in the dressing. The ascaris was supposed to have passed through the gastroenterostomy and cholecystgastrostomy stoma into the gall bladder and bile ducts and thence through the ligatured end of the common bile duct, carrying the ligatures with it. After 4 weeks the bile flow ceased but the pancreatic flow continued. After 2 months the patient went home with a rubber tube draining pancreatic juice into a receptacle, which was emptied every few hours. Three months after the operation a jejunostomy was done and the pancreatic juice was injected into the jejunum. Later the drainage tube was connected with the jejunostomy tube, thus permitting the pancreatic juice to flow directly into the jejunum. Further progress of this patient has not been reported.

The patient operated upon by Brunschwig drained a clear serous fluid from the wound for a few days followed by a discharge of bile. The biliary drainage reached a maximum of 560 cubic centimeters daily during a period of 44 days, and then gradually diminished and became mucoid. The fluid contained food particles, indicating an intestinal fistula. Efforts to close the fistula by injection of kaolin and zinc oxide paste failed. A small fistula leading from the inverted end of the duodenal stump persisted until death. Although no metastases were found at the operation, the patient died of general carcinomatosis of the peritoneal cavity and metastases to the liver 85 days following the excision.

Trout's patient was operated upon in one stage. Death occurred in 6 to 8 hours, apparently from shock. Trout doubts the advisability of attempting the operation in one stage.

Detailed reports of the cases operated upon by Janes, Hollenberg, Schullinger, Janssen, and Whipple are not available. The results of these operations appear in Table I.

On the fourth day following the first stage of the operation Crile's patient had a hemorrhage into the intestine which was treated by several transfusions. Some fever followed which was attributed to a mild cholangitis. The cholangitis continued after the discharge of the patient at the end of 3 weeks. The night after the second operation the temperature rose to 106 degrees F. and on the following day the patient had a chill, and the icterus index rose to 25 units. This was considered a recurrence of the cholangitis. A blood culture was positive for Bacillus coli. On the ninth postoperative day bile and a dye given by mouth appeared on the dressings indicating that

TABLE I—LIST OF REPORTED CASES OF RESECTION OF THE DUODENUM AND HEAD OF THE PANCREAS

Authors	Year Age Sex	Duration of symptoms	Origin of tumor	Result
Whipple, Parsons and Mullins	1935 53 M	2 mos.	Ampulla	Lived 8 mos. Died of stenosis of cholecystgastrostomy
Whipple, Parsons and Mullins	1925 49 M	2½ mos.	Ampulla	Died 32 mos. after operation with liver metastases
Orator	1936 48 F	2 mos.	Papillen-pancreas-kopfkarcinoms	Alive after 3 mos. No later report
Brunschwig	1937 60 M	2 mos.	Ducts in pancreas	Died 85 days after operation of general carcinomatosis
Trout (Reported by Whipple)	1938 53 M	?	?	Died of shock a few hrs. after completion of operation in one stage
Janes (Reported by Whipple)	1938 ? ?	?	?	Died of pneumonia on fifth postoperative day
Janes (Reported by Whipple)	1938 ? ?	?	?	Operation successful. Late result unknown
Hollenberg (Reported by Whipple)	1938 ? ?	?	?	Alive after 4 mos. No later report
Schullinger (Reported by Whipple)	1938 ? ?	?	?	Died of pneumonia on second postoperative day
Janssen (Reported by Whipple)	1938 ? ?	?	Head of pancreas	Died on 10th postoperative day of asthenia and biliary fistula
Whipple	1938 ? ?	?	?	Died of subphrenic abscess on sixteenth postoperative day
Whipple	1938 ? ?	?	?	Lived 8 mos. Died of liver metastases*
Crile	1938 37 M	5 mos.	Bile or pancreatic ducts	Lived 6 mos. Death due to stenosis of cholecystgastrostomy stoma
Illingworth	1939 59 M	1 mo.	Probably ampulla	Died 43 days after operation with bile peritonitis
Orr	1940 47 M	5 mos.	Ampulla	Alive after 6½ mos. Has pancreatic and small intestine fistulae

*Personal report by Doctor Whipple.

a gastric fistula had developed. On the eleventh postoperative day there was profuse bleeding into the fistulous tract with the formation of a large hematoma in the abdominal wall. This hematoma later became infected. The patient recovered and the fistula closed within 2 months. Death occurred after 6 months due to stenosis of the cholecystgastrostomy stoma.

Illingworth's patient developed a wound infection which delayed the second stage operation. During the operation a ligature slipped off the end of the common duct which was so short that suturing was necessary. The immediate postoperative course was uneventful and the patient was out of bed in 14 days and went home in good condition. Five weeks later he developed severe abdominal pain, distention, and fluid in the abdominal cavity. Exploration was done and bile peritonitis found. Death occurred on the forty-third postoperative day as a result of bile peritonitis due to leakage from the sutured end of the common duct. The author attributes the death to a technical error in closing the severed common duct. He suggests that in the future he would implant the cut end of the common duct in the stomach.

RESULTS

Five of the 15 patients here reviewed and reported died as a result of the operation, an immediate mortality of 33.3 per cent. Three deaths were due to metastases, 2 to stenosis of the cholecystgastrostomy stoma, 1 to bile peritonitis, and 4 were alive at the time of the last report.

The effect that this operation may have upon the liver has not yet been determined. Berg and Zucker have demonstrated early degenerative changes and fatty infiltration of the liver in depancreatized dogs. They also noted extensive fatty infiltration after obstruction of the pancreatic ducts for 80 days. Dragstedt has confirmed the observation that depancreatized dogs develop fatty infiltration of the liver. These changes he has been able to prevent by administering the pancreatic hormone lipocaic. The experiments of Boyce indicate that fatty changes in the liver develop after complete or partial pancreatectomy but do not occur when the pancreatic ducts are severed and ligated with the pancreas left *in situ*. These authors suggest that in clinical cases fatty infiltration of the liver is not likely to develop when radical surgery is done for removal of the ampulla without reimplantation of the pancreatic ducts or excision of pancreatic tissue. If the head or head and body of the pancreas are excised fatty infiltration will develop. Cole has called attention to fatty infiltration of the liver associated with pancreatic fibrosis. Snell and Comfort report cases of pancreatic lithiasis as a probable cause of fatty changes in the liver. With this evidence it would be logical to assume that fatty infiltration of the liver might result from resection of the head of the pancreas and obliteration of the pancreatic ducts although Whipple (14) did not find such changes at necropsy of a patient who lived 8 months after the radical removal of the duodenum and head of the pancreas.

CONCLUSIONS

The record of patients operated upon by excision of the duodenum and head of the pancreas has been disappointing.

The plan of the operation is fundamentally sound even if the administration of lipocaic may prove to be necessary to maintain life.

A study of many more patients operated upon by this technique will be necessary before the value of the procedure can be determined.

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THE PROBLEM OF CARCINOMA OF THE CARDIAC END OF THE STOMACH

JOHN H. GARLOCK, M.D., F.A.C.S., New York, New York

THE recently increasing incidence of successful resections for cancer of the esophagus has been a large factor in awakening interest in a problem in surgery which has received scant attention by the surgical profession in the past two or three decades. It is quite true that, in spite of rapid advances in the diagnostic methods of roentgenography, esophagoscopy, and gastroscopy, and improvement in surgical technique, surprisingly few attempts have been made to treat cancer of the cardiac end of the stomach by surgical means. While volumes have been written on the subject of cancer of the stomach, the scarcity of literature pertaining to neoplasms of the cardia is noteworthy. Sustained interest on the part of the medical profession in a subject such as the surgical treatment of cancer must be maintained by repeated reports of encouraging progress. At the risk of appearing repetitious, I would like to report my experience with the surgical treatment of this disease, emphasizing the fact that the diagnostic and pathological features may be quite different from those encountered in cancer of the thoracic esophagus.

From an anatomical standpoint, the cardia of the stomach may present considerable variation in size, position and shape (Fig. 1). In most individuals, the terminal one-half inch of esophagus occupies an intra-abdominal position just below the diaphragm and is known as the cardiac antrum. The mucous membrane is lined by stratified squamous epithelium. The junction of esophagus and stomach is sharply demarcated and distinct. It is indicated on the greater curvature side by an indentation called the incisura cardiaca. The musculature and mucus membrane of the stomach are thickened at the point of union with the esophagus to form a cardiac sphincter mechanism. The pars cardiaca is that part of the stomach at and just beyond the point of union with esophagus and extends over to the greater curvature side to the upper part of the fundus. The cardiac orifice of the stomach is situated at the level of the eleventh thoracic vertebra behind and the seventh left chondrosternal junction in front. The mucous membrane of the cardia has the same columnar epithelium as the remainder of the stomach. It is important to remember that new growths in this region form adenocarcinomas in contradistinction to the squamous cell tumors arising in the esophagus.

The lymph node drainage from the cardiac end of the stomach may present considerable variation (Fig. 2). In general, the initial direction of spread is toward the nodes in the gastrohepatic omentum and also those located along the greater curvature near the incisura cardiaca. There may be further extension to the peripancreatic nodes. The latter, in my experience, is unusual. In general, it may be said that adenocarcinomas arising at the cardia spread peripherally *below the diaphragm* toward the gastrohepatic or gastrocolic lymph nodes, depending upon the location of the tumor with respect to the lesser or greater curvature. However, on at least two occasions, I have seen extensive involvement of the nodes in the posterior mediastinum *above the diaphragm* with no enlargement of the nodes below the diaphragm. On the other hand, I have, in one case, demonstrated extensive involvement of the gastrohepatic nodes and also the liver where the primary growth was a squamous cell carcinoma located in the esophagus just above the diaphragm. I believe that experience with a great number of operative cases will demonstrate whether or not these are rare exceptions to the generally accepted interpretation of lymphatic spread from the two areas under discussion. Certain it is that early metastatic involvement of the liver is a frequent finding. It is not uncommon to discover metastatic nodules in the liver and no palpable lymph node extension. This early extension to the liver is unpredictable and is dependent upon chance invasion of the gastric veins by tumor growth and extension to the portal system.

The symptoms produced by a new growth at the cardia of the stomach will in large part depend upon the exact site of origin of the tumor and the direction of its growth. Neoplasms arising at the cardiac orifice quickly interfere with the normal act of deglutition and produce symptoms of lower substernal pain, especially on swallowing. The

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growth usually extends upward to involve the lower esophagus. On the other hand, a tumor originating on the greater curvature side of the cardia near the so called silent area of the stomach may produce no symptoms whatever until it extends into the orifice itself, when difficulty in swallowing will be noted. By the time dysphagia is noted, the growth may very well have reached the inoperable stage. It is this type of case that renders the whole problem discouraging. However, it is important to stress that many of these patients may have persistent indigestion which resists ordinary medical treatment or that there may be an unexplained loss of weight. Under such circumstances, it is imperative that the physician avail himself of every diagnostic method in order to demonstrate the presence of a tumor in this region. In the main, the symptoms will depend upon the proximity of the tumor to the stream of swallowed food and the size of the growth with respect to diminution of caliber of the cardiac orifice or lower esophagus. In Case 15 in the group reported herewith, there was no difficulty in swallowing, although the tumor had grown upward to involve the lower esophagus. This was due to the fact that there was little diminution in the caliber of the cardiac orifice.

The question of loss of weight is of considerable importance to the surgeon in aiding him to estimate the probable operability of the tumor. A critical analysis of the cases reported in this paper indicates that loss of weight does not reach the extremes frequently seen in operable squamous cell cancer of the esophagus and that, when great weight loss has occurred, the tumor, in all probability, will be found to be inoperable either because of extensive node involvement or by reason of extension to the liver. Therefore, in most instances, in which a resectable growth is a probability on exploration, a preliminary jejunostomy for feeding purposes will be found unnecessary.

The symptom of persistent back pain merits some discussion. Pain in the back, of a fairly constant and dull variety and located to the left of the midline on a level with the eleventh or twelfth thoracic vertebra, is usually not an early symptom. Correlation of this symptom with the operative findings indicates its cause to be due usually to direct extension of the new-growth to the posterior parietes or to the body of the pancreas, rather than to a perigastric inflammatory reaction frequently seen with cancers in other parts of the stomach. It seems to me that this is of considerable importance in estimating operability at the time of exploration.

Possible malignant degeneration of a pre-existing benign ulcer at the cardia is of considerable interest. There were three instances in this series of a long-standing ulcer history with relief of symptoms by the usual medical therapy and in one of these the x-ray films taken 10 years previously showed clearly a small penetrating ulcer at the lesser curvature side of the cardia. In the latter case, symptoms became more persistent in the last few months and did not respond to medical therapy. While the clinical and pathological evidence of malignant degeneration of a pre-existing ulcer in these three instances is more speculative than real, the course of events in each case is certainly very suggestive.

The general examination of a patient suspected of harboring a carcinoma of the cardia rarely yields positive findings. Occasionally, one may find an enlarged lymph node in the left supraclavicular region, the so called Virchow node. Unusual hardness of this gland or fixation to surrounding tissues are indications for biopsy to demonstrate metastatic involvement. Rarely can one palpate the tumor on abdominal examination. Metastatic liver involvement may or may not be demonstrated by palpation. It is important not to omit rectal examination to exclude metastases to the rectal shelf.

It seems needless to stress that any patient presenting the symptoms enumerated should be referred to a competent radiologist for roentgenographic visualization of the esophagus and stomach. In most instances, the presence of a tumor will be clearly demonstrated by the usual methods of examination. Obstruction of the lower esophagus, irregular filling defects at the cardia, rigidity of the lesser curvature side of the cardia on fluoroscopic observation and loss of the normal mucosal pattern are among the usual roentgenographic findings. Not infrequently, it may be very difficult for the radiologist to demonstrate any abnormality. This is especially true when the tumor, usually a small one, is located on the posterior wall toward the incisura cardiaca. Persistency on the part of the examiner will, in most cases, demonstrate the growth. This will require a heavier mixture of barium and the taking of multiple films in lateral, oblique, reclining, and standing positions.

Roentgenographic examination should be followed, in every instance, by esophagoscopy. This is a most important part of the complete work-up, because the esophagoscopist is able to locate accurately the upper level of the tumor with respect to the distance from the upper incisor teeth, and thereby guide the surgeon in the choice

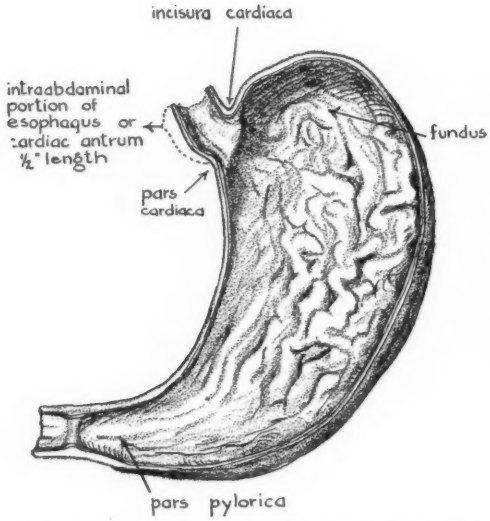

Fig. 1. Drawing of the posterior half of the stomach, interior surface, showing the anatomical relationship of the cardiac antrum, cardia, and fundus.

of his operative approach. Histological examination of the biopsy specimen which should be secured in every case will indicate the origin of the tumor from either the esophagus or the cardia.

The finding of adenocarcinoma on microscopic examination indicates origin from the cardia and will make for an altogether different plan of surgical attack than that employed when the histological picture is one of squamous cell cancer. This will be referred to later.

Up to the present time, I have preferred esophagoscopy to gastroscopy because, with the former, more accurate visualization of the tumor may be obtained and, at the same time, a biopsy specimen may be secured. In the hands of a competent operator, there is little difference in the relative risk of the two procedures.

In previous publications, I have stressed the importance of preparing these patients thoroughly for the operative ordeal. It is unnecessary at this time to elaborate on the details. Suffice it to say that this preparation should include careful attention to oral hygiene, a high caloric liquid diet containing the necessary vitamins and minerals, administration of fluids by venoclysis and a pre-operative transfusion of whole blood. In addition, as a result of our favorable experiences with the pre-operative administration of sulfanilamide in colon surgery, I have routinely administered this drug to the patients with cancer of the cardia for 72 hours prior to operation. It is my impression that this drug is a considerable factor in minimizing infection.

The finding of adenocarcinoma in the biopsy specimen should at once indicate to the surgeon the plan of surgical attack to be adopted. I believe that there is general agreement at the present time that the operation of choice for cancer of the lower esophagus and cardiac end of the stomach with secondary esophageal extension is a left transthoracic, transdiaphragmatic resection with intrathoracic esophagogastrostomy. I believe that the combined abdominal and thoracic approach of Marwedel and the free thoracolaparotomic technique of Ohsawa are procedures of shocking magnitude compared with the transpleural operation. Because the lymphatic spread of cancers of the cardia is in a peripheral direction *below the diaphragm* in most instances, it is important to determine operability without exposing the patient unnecessarily to the risks of a transthoracic exploration. For this reason, I recommend that exploration be carried out through a small upper left rectus incision. Palpation will quickly indicate whether the tumor is resectable. Metastases to the liver or to the pancreatic lymph nodes and fixation of the growth to neighboring vital structures are contraindications to further surgery.

If the tumor seems operable, the wound may be closed quickly with through and through steel wire sutures. The patient is now turned on his right side and, with a complete clean operative setup, the left thoracic cavity is entered through the eighth interspace. The details of the operative procedure have been described in previous publications and will, therefore, not be elaborated upon at this time. Briefly, the operation, a modification of the original Fischer and Sauerbruch procedures, includes division of the eighth, seventh, and sixth ribs close to the spine, mobilization of the distal esophagus, radial incision of the left leaf of the diaphragm, mobilization of the upper two-thirds of the stomach, resection of the tumor bearing portion, the performance of a two layer silk suture anastomosis between the end of the esophagus and the anterior wall of the stomach, and the telescoping of the esophagus into the stomach in order to minimize tension on the suture line. Under water drainage of the pleural cavity by a tube inserted through a stab wound in the subjacent intercostal space completes the operation. I believe that every patient should be transfused during the course of the operation. In every case, I have employed posi-

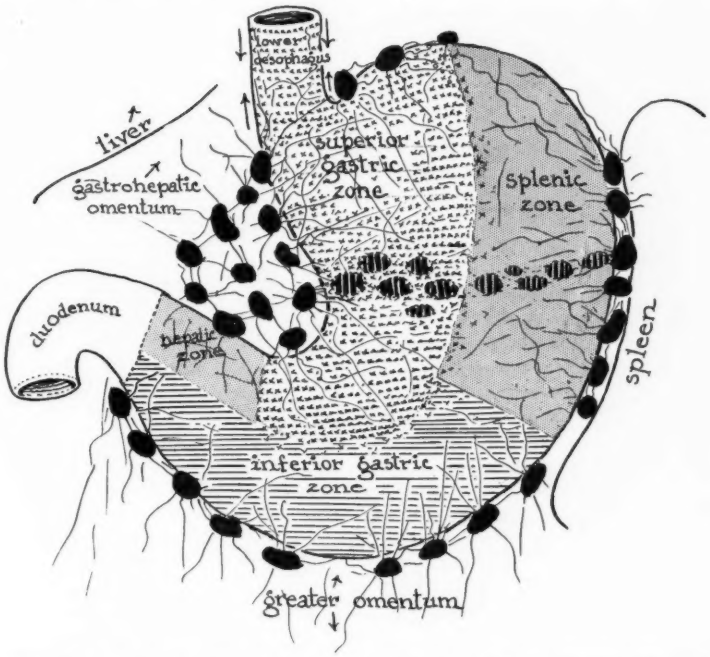

Fig. 2. Composite drawing of the lymph node drainage of the stomach taken from Poirier, Bouviere, and Cunningham, and the postmortem studies of cases of carcinoma of the cardia at Mt. Sinai Hospital.

tive pressure ethylene or cyclopropane anesthesia following a basal dose of avertin.

POSTOPERATIVE CARE

Before the operation is undertaken, it is important to explain to the patient that he must not swallow for a period of 4 or 5 days. The processes of repair at the suture line will be hastened by the full co-operation of the patient in this respect. Fluids are administered by a continuous intravenous drip of 5 per cent glucose in normal saline.

The character of the material draining through the intercostal tube will indicate the progress of the intrathoracic situation. During the first 48 hours, the fluid is sanguineous. After this, it gradually assumes a lighter color and decreases in amount until the seventh or eighth day when the tube may be removed.

Small sips of water may be given on the fourth or fifth day. Increasing amounts of liquid are given until the twelfth or thirteenth day when custards, gelatins, cereals, etc., are permitted. The diet is rapidly increased thereafter. Solid food should not be given until the third week.

RESULTS[1]

During the past 3 years I have operated upon 15 patients with adenocarcinoma of the cardiac end of the stomach. Five of this group were found to be operable, an operability percentage of 33.3. There was no operative mortality in the inoperable group. Five patients were subjected to the operation of resection and intrathoracic esophagogastrostomy. Two of these succumbed: one, Case 3, of a cerebral hemorrhage on the third day and the other, Case 5, of inanition and old age debility on the fourth day. The operative mortality was 40 per cent.

The status of the 3 patients who recovered is as follows: One, Case 6, was well for 1 year when he began to develop symptoms of a local recurrence. At the present time, 16 months after operation, there is obvious metastatic liver involvement and the patient is failing rapidly. The second patient,

[1] Since submitting this paper for publication, I have explored 10 additional cases, making a total of 25. In the entire series, 9 were found operable, an operability rate of 36 per cent. There were 4 postoperative deaths, an operative mortality of 44.4 per cent. Of the 5 survivors, 1, Case 6 in the paper, died of retroperitoneal metastases 1½ years after the operation. The 4 remaining patients are alive and well (no evidence of recurrence) 13 months, 1 year, 3 months, and 3 months, respectively.

Case 12, is alive and well 5 months after operation. The third patient, Case 15, is alive and well 4½ months after operation.

Statistics, especially in a small series of cases, ordinarily have very little value. However, in a field of surgery such as the one under discussion, they are of considerable importance from the standpoint of indicating whether encouraging progress is being made. In addition, they indicate the risk of subjecting a patient to an extensive procedure. It is particularly important, especially in a small series, to stress that survival statistics may be materially influenced by the recovery or death of one patient.

With a disease such as cancer, there can be no half-hearted policy with respect to treatment, especially as far as our present knowledge of it is concerned. If a patient with an operable carcinoma of the cardia can be offered a 60 per cent chance of surviving an attempt at radical removal, then, I believe the risk should be undertaken. This presupposes the careful preoperative preparation and postoperative care, as already outlined. In most instances, operability must be determined by an exploration of the upper abdomen and, according to the experiences reported in this paper, the risk of this procedure is negligible.

CASE REPORTS

Case 1. C. D., male, age 56 years, was admitted to New York Hospital January 19, 1938. His past history showed that in January, 1921, he had had an operation for duodenal ulcer. This consisted of a posterior gastroenterostomy and an appendicectomy. For the succeeding 8 years the patient remained in good health. He gained considerable weight during this period, finally reaching 208 pounds. He then began to experience difficulty with digestion which consisted of "sour stomach" accompanied by vomiting. Occasional black stools were noted.

In May, 1931, a gastrointestinal roentgenological examination was made. The patient was told he needed another operation. He refused to have this done. Medical treatment was given at the time, with considerable relief. He had mild recurrences of epigastric distress during the intervening years.

In August, 1937, he began to experience difficulty in swallowing, and in the space of 2 weeks lost 12 pounds. This difficulty became worse until he was able to ingest fluids only. At no time had he experienced any pain.

Physical examination revealed a well-developed male. The heart and lungs were negative. There was a small upper right rectus scar. Roentgenological examination of the esophagus and stomach disclosed an irregular filling defect at the lower end of the esophagus just above the cardiac end of the stomach, with obstruction at the gastroenterostomy stoma. The barium, however, was seen to pass through the duodenum without difficulty. There was a small 24 hour residue.

On January 26, 1938, esophagoscopy disclosed marked stenosis of the esophagus due to a mass projecting into the lumen at a point 38 centimeters from the upper incisor teeth. This placed the lesion just above the cardiac end of the stomach. Microscopic examination of the biopsy specimen taken at this time revealed papillary adenocarcinoma of the esophagus. Laboratory examinations were negative.

Operation was performed February 1, 1938—a Janeway gastrostomy. Because of the previous operation, numerous adhesions were encountered. Careful palpation of the upper end of the stomach and the upper aortic lymph nodes failed to reveal anything suggesting new-growth or metastatic involvement of the nodes. Because the roentgenological examination disclosed patency of the duodenum, a gastrostomy was performed in the hope that the feedings would emerge from the stomach by the normal route.

Convalescence following this procedure was complicated by a severe lobar pneumonia involving the left lower lobe. Considerable difficulty was encountered because of reflux of gastric contents at the time of feeding. To overcome the obstruction to the flow of gastric contents through the gastroenterostomy stoma, a cystoscope was passed into the stomach through the gastrostomy opening and a small catheter was inserted through the stenotic gastroenteric stoma into the jejunum. Following this procedure the administration of feedings was greatly simplified. The patient's general condition improved and there was a considerable gain of weight.

A second operation was done on April 19, 1938. A left transpleural approach was employed. There were numerous adhesions binding the lobes of the lung to the parietal pleura and diaphragm. The mediastinum was opened and there was disclosed a neoplasm of the esophagus involving the distal 4 inches of this organ and extending through the diaphragm into the stomach. The mass was intimately adherent to the aorta and the opposite mediastinal pleura. It was considered inoperable. The chest was closed in the usual manner.

Convalescence following this procedure was uneventful. The wound healed by primary union. The patient gradually went down hill, and died of his disease at the end of May, 1938.

Case 2. E. L. S., male, age 36 years, was admitted to Mt. Sinai Hospital, complaining of difficulty in swallowing for about 2 months. During the 6 or 7 months prior to admission, he had noted a peculiar "bursting" sensation behind the lower sternum soon after eating. This symptom had become more pronounced during the previous 2 months and was accompanied by dysphagia. During the last few weeks, he was able to swallow liquids only. Anorexia and weakness were prominent symptoms. Weight loss amounted to 12 pounds. The past history was negative.

Physical examination disclosed the following: The patient had a moderate anemia and was cachectic. There were no abdominal masses and the liver was not enlarged. There was no lymph node enlargement. Hemoglobin was 77 per cent. Red blood cells numbered 4,320,000; the white blood cells were normal. Roentgenological examination disclosed an obstructing lesion of the esophagus beginning about 2 inches above the diaphragm. Esophagoscopy (Dr. R. Kramer) showed a friable, bleeding mass in the esophageal wall starting at 37 centimeters from the incisor teeth. Microscopic examination of the biopsy specimen revealed adenocarcinoma.

Operation was performed on October 19, 1938. Following a preliminary transfusion, the cardia was approached through the usual left transpleural route. A very firm tumor involving the lower 2 inches of the esophagus and extending through the diaphragm into the cardiac end of the stomach was found. The tumor was solidly attached to the vertebral column and right mediastinal pleura and was, therefore, considered inoperable. The thoracic wound was closed and a Witzel gastrostomy was performed.

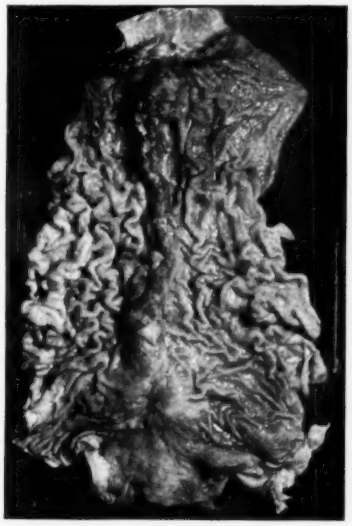

Fig. 3. Left, Case 3. Resected cardia of stomach and lower esophagus. The lymph nodes along the lesser curvature showed metastases.
Fig. 4. Case 3. Postmortem specimen showing intact suture line.

CASE 3. J. A., male, age 49 years, was first seen January 18, 1939. He complained of upper abdominal pain of 5 years' duration. He had been under the care of numerous physicians, and many roentgenological examinations of the gastrointestinal tract had been made. He was told he had an ulcer of the stomach, and was treated medically with only transient relief. The course of events in this case suggested malignant degeneration of an old gastric ulcer, situated at the cardia. During the last 3 months, he noted persistent pain in the epigastrium radiating to the back, accompanied by marked weakness. At no time was there any dysphagia. There was a weight loss of 8 pounds. The past, personal, and family history was negative.

Physical examination revealed a rather pale, thin adult male. Heart and lungs were negative. There were no palpable masses in the abdomen and the liver was not enlarged. No enlarged lymph nodes were found. Roentgenological examination disclosed an irregular filling defect at the cardia, which extended upward and involved the lower 2 inches of the esophagus without, however, producing any obstruction. Esophagoscopy revealed a friable, ulcerating tumor beginning 37 centimeters from the incisor teeth. The biopsy specimen showed adenocarcinoma.

The patient was admitted to Mt. Sinai Hospital, January 24, 1940. Laboratory examinations showed a negative Wassermann. The urine was negative. Hemoglobin was 50 per cent; red blood cells, 3,100,000.

Operation was performed January 26, 1940. The anesthesia used was avertin-ethylene. After a preoperative transfusion of 500 cubic centimeters of blood, an incision was made in the eighth left interspace with division of the eighth, seventh, and sixth ribs close to the spine. Exposure of the lower esophagus revealed a tumor mass occupying the distal inch of the organ and extending into the cardia. The diaphragm was split radially outward from the hiatus, and exploration of the upper abdomen disclosed a normal liver and a few enlarged nodes adjacent to the cardia on the lesser curvature side. There were no enlarged nodes in the mediastinum. Resection of the tumor was carried out after mobilization of the upper stomach and lower esophagus. The upper half of the stomach was then brought into the thoracic cavity and an end-to-side anastomosis effected between the esophagus and stomach, by means of fine silk throughout. The stomach wall was drawn over the suture

Fig. 5. Case 5. Tumor-bearing portion of cardia and lower esophagus resected at operation.

Fig. 6. Case 6. Preoperative roentgenogram showing deformity at the cardia and obstruction in the lower esophagus.

line and anchored to the mediastinal pleura and cut edges of the diaphragm in order to eliminate tension on the suture line. The phrenic and vagus nerves were not disturbed. The incision in the diaphragm was now repaired and the cut edges were sewn to the stomach wall. An under-water drainage tube was inserted through a stab wound in the subjacent intercostal space, and the operative wound was closed in the usual manner. The lung was now inflated. During the course of the operation, the pulse varied between 96 and 128, and the systolic blood pressure between 136 and 98. A transfusion of 500 cubic centimeters of blood was given during the operation, which took 2 hours and 20 minutes.

Pathological examination. The gross specimen revealed an infiltrating adenocarcinoma of the cardia with involvement of the lower esophagus. Metastatic deposits were found in the lymph nodes along the lesser curvature of the excised specimen (Fig. 3).

During the first 2 postoperative days, the patient's course was most satisfactory. Pulse varied between 80 and 120; respirations, 24 to 30; temperature 100 to 102 degrees F. Fluids were administered by continuous intravenous drip. On the third postoperative day, the patient suddenly became comatose, the temperature mounted to 108 degrees F., and there were signs of a complete right hemiplegia. Notwithstanding active therapy, the patient's condition rapidly became worse, and he expired during the evening of the third day.

Autopsy examination revealed a completely expanded left lung; no evidence of infection; and an intact water-tight suture line (Figs. 3 and 4). Death was due to a hemorrhage at the internal capsule of the brain.

Case 4. M. B., female, age 70 years, was first seen January 18, 1938. She complained of epigastric distress of 10 months' duration. The pain was experienced immediately after eating and was accompanied by hiccup. Some

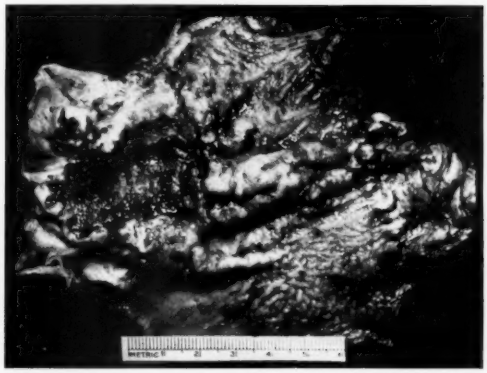

Fig. 7. Case 6. Photograph of operative specimen.

relief had been obtained by a dietary regimen. During the last 3 or 4 months, she experienced increasing difficulty in swallowing solid food. On a few occasions, she had noted blood in the stool. She had lost 30 pounds in weight. The past and personal histories were irrelevant.

Physical examination revealed a remarkably well preserved woman. Heart and lungs were negative. Blood pressure was 160/90. No enlarged lymph nodes were present. There was resistance in the epigastrium, but a mass could not be felt. The liver was not enlarged.

She was admitted to Mt. Sinai Hospital January 21, 1938. Roentgenological examination showed the presence of a mass at the cardiac end of the stomach which extended upward and involved the lower esophagus. Aside from a mild anemia, the laboratory examinations were negative.

Operation was performed January 29, 1938, under avertin-ethylene anesthesia. A small upper left rectus incision was made. Abdominal exploration was undertaken first in order to determine operability. There was found a large tumor mass involving the cardia and lower esophagus. In addition, large packets of involved nodes were found overlying the aorta. The lesion was obviously inoperable. A Janeway gastrostomy was performed. The patient left the hospital and succumbed to her disease 4 months later.

Case 5. L. E., female, aged 73 years, was first seen July 28, 1939. She complained of pain behind the lower sternum when eating, which had been present for over 3 months. This was frequently accompanied by hiccups. Two and one-half months ago, she noted that swallowed food seemed to stop at the point of pain. Dysphagia became increasingly more severe until she was able to swallow only liquids. The weight loss was 14 pounds. Past history was negative.

Physical examination revealed an elderly woman, in excellent general condition; heart and lungs were negative; blood pressure was 160/88; abdomen, negative; no enlarged lymph nodes. She was admitted to Mt. Sinai Hospital, where a work-up disclosed hemoglobin 90 per cent; red blood cells, 5,150,000. Urinalysis and Wassermann were negative. Roentgenological examination disclosed an obstructing neoplasm in the lower esophagus just above the diaphragm, with irregular filling of the cardia. Esophagoscopy (Dr. R. Kramer) showed an almost completely obstructing tumor, beginning 38 centimeters from the incisor teeth. The biopsy specimen showed an adenocarcinoma.

Operation was performed August 3, 1939. Under avertin-ethylene anesthesia, a left transthoracic approach was made through the ninth interspace. There was found an

annular constricting tumor at the lower end of the esophagus and cardia of the stomach, measuring 2 inches in length. The liver was normal and no enlarged nodes were felt. The tumor bearing portion of stomach and esophagus was resected and an intrathoracic end-to-side esophagogastrostomy was carried out (Fig. 5) as described. An underwater drainage tube was inserted in the subjacent intercostal space. A transfusion of 500 cubic centimeters of blood was given during the operation. The patient stood the procedure very well. The pulse rate varied between 90 and 110. The systolic blood pressure was fairly steady at 140. Time, 2 hours and 25 minutes.

The immediate postoperative course was devoid of any untoward incident. The highest temperature, 102.6 degrees F., was noted on the third day. The pulse varied between 88 and 110, the respirations between 16 and 26. Fluids were administered intravenously. By the end of the third day, it was noted that the patient was apathetic and listless. This became more pronounced until definite coma developed on the fourth day. The patient succumbed during the evening of this day, with a terminal fever of 100 degrees F.; a pulse of 100; and respiratory rate of 16.

Postmortem examination was completely negative, except for a small localized abscess in the lower mediastinum near the suture line. The latter was quite intact. No remaining carcinoma was found.

CASE 6. W. H., male, aged 49 years, was first seen June 14, 1939. He complained of dysphagia of 6 weeks' duration and stated that swallowed food stopped at about the level of the ensiform cartilage, remained there a few moments, and then passed on into the stomach. There was no regurgitation. Fluids were swallowed with ease. The weight loss was 5 pounds.

Physical examination disclosed a well nourished individual, apparently in good health. There were no abnormal findings. Roentgenographic examination of the esophagus showed an obstructing neoplasm at its lower end, involving also the cardia (Fig. 6). He was admitted to Mt. Sinai Hospital, where esophagoscopy (Dr. R. Kramer) showed an ulcerating, obstructing tumor, beginning at 40 centimeters from the incisor teeth. The biopsy specimen showed a mucous cell carcinoma. All laboratory examinations were negative.

Operation was done June 20, 1939, under avertin-ethylene anesthesia. Left transthoracic approach was made through the eighth interspace. There was found a constricting, annular tumor involving the distal 2 inches of esophagus and extending into the cardiac end of the stomach for about 1 inch. Abdominal exploration through an incision in the diaphragm revealed a normal liver, but a number of enlarged, firm nodes in the gastrohepatic omentum and also along the greater curvature in the region of the cardia. Operation consisted of a radical resection of the lower esophagus and upper stomach with removal of as much of the gastrohepatic and gastrocolic omenta as was possible. An intrathoracic esophagogastrostomy was performed.

Pathological examination of the excised specimen showed an infiltrating mucous cell carcinoma of the cardiac end of the stomach with involvement of the lower end of the esophagus. All the excised lymph nodes showed metastatic involvement (Fig. 7).

The immediate postoperative course was uneventful. There was an initial rise of temperature to 103.4 degrees F. The patient's general condition was excellent. The swallowing of fluids was started on the sixth day. The intercostal drainage tube drained gradually diminishing quantities of serosanguineous fluid until the eighth day, when the tube was removed. The operative wound healed by primary union.

Fig. 8. Case 6. Roentgenogram of esophagus and stomach, taken 7 months after operation, showing intrathoracic position of upper stomach, (slightly retouched).

The postoperative elevation of temperature which usually persists in these cases until about the fifth day, did not subside, and remained elevated between 102 and 103 degrees F. Repeated examinations finally disclosed the presence of fluid at the right base in front and laterally. This was confirmed by roentgenological examination. Repeated aspirations were negative. There was no cough or expectoration. For a fleeting moment on the tenth day, it was thought that the breath was foul. The patient presented a peculiar dyspnea without cyanosis. The respiratory rate ranged between 26 and 40. On the twelfth day, the patient suddenly went into profound shock, with marked dyspnea, cyanosis and severe respiratory embarrassment. The physical signs were those of air and fluid in the right pleural cavity. Aspiration of the chest showed putrid air and pus to be present. An immediate wide thoracotomy was performed under local anesthesia. The patient had apparently ruptured a postanesthetic lung abscess which was peripherally located and which had not made itself manifest by the usual foul breath and sputum. The pleural effusion originally noted was of the sympathetic variety.

Convalescence following this operation was slow but progressive. The right lung expanded completely, and the wound finally healed. The patient was discharged from the hospital at the end of the sixth week.

There was a rapid gain in weight. The patient was able to swallow all types of food without difficulty until about the fourth month, when it became apparent that a stricture was forming at the site of anastomosis. Esophagoscopy showed a tight stricture at the site of the suture line. In performing a biopsy at this point, Dr. Kramer removed the

Fig. 9. Case 12. Preoperative roentgenogram showing irregular, stenosing filling defect in lower esophagus and cardia.

silk thread which had been used to effect the anastomosis. Thereafter, the orifice widened rapidly and no further dilatation became necessary (Fig. 8).

The patient was well until 1 year after operation. At that time, he began to experience mild substernal pain on swallowing. Esophagoscopic examination disclosed a small flat tumor on the posterior esophageal wall, about 2 centimeters above the anastomosis. A biopsy specimen showed the same histological features of carcinoma as the original growth. Dr. Kramer inserted a few radium seeds in the hope of checking this lesion. However, at the present writing, 16 months after the original operation, the patient is failing slowly and losing weight. The outlook seems hopeless.

Case 7. J. B. male, aged 62 years, was first seen September 27, 1939. He stated that his present illness had started 4 months before, with indigestion and belching of gas. There was no pain until the beginning of September, when he noted retrosternal distress on swallowing. He vomited occasionally, and was unable to swallow solid food. He had lost 20 pounds.

Physical examination revealed an elderly man in excellent general condition. The liver was not enlarged. There were no abdominal masses or enlarged lymph nodes. Roentgenographic examination showed a filling defect at the cardiac orifice, with marked obstruction of the lower end of the esophagus. The latter structure was markedly dilated above the obstruction.

The patient was admitted to Mt. Sinai Hospital, where esophagoscopy disclosed an obstructing neoplasm, starting at 40 centimeters from the upper incisor teeth. There was a moderate anemia.

Operation was performed October 5, 1939, under avertin-ethylene anesthesia. As recommended in the body of this paper, an abdominal exploration was carried out through a small upper left rectus incision. A tumor mass, located in the cardia and extending into the esophagus was found. It would have been considered operable were it not for the fact that metastatic nodules were found in the liver. A Janeway gastrostomy was performed. The patient left the hospital, and died 5 months later of his disease.

Case 8. W. C., male, aged 47 years, was admitted to Mt. Sinai Hospital, October 20, 1939. He stated that for the past 4 years he had experienced recurrent episodes of postprandial epigastric pain, relieved usually by medication and dietary restriction. During the past 4 months he had steady, dull pain in the epigastrium with a sense of fulness and gradually increasing difficulty in swallowing solid food. He had lost 40 pounds.

Physical examination disclosed the following: The patient showed a marked recent weight loss. Heart and lungs were negative; abdomen, negative; laboratory examinations, negative. Roentgenographic examination showed a large filling defect at the cardiac orifice of the stomach, with extension to the lower esophagus. Esophagoscopy (Dr. J. Goldman) revealed a firm, ulcerating tumor, starting at 39 centimeters from the incisor teeth. A biopsy specimen showed adenocarcinoma.

Operation was done October 25, 1939, under avertin-cyclopropane anesthesia. Exploration of the upper abdomen was carried out through a small left rectus incision. A tumor mass was found extending from the esophageal hiatus downward along the lesser curvature for about 2½ inches. The tumor was movable and there were no enlarged nodes or palpable nodules in the liver. The tumor was considered operable. Therefore, the left thoracic cavity was opened through the eighth interspace. Exploration revealed a very extensive involvement of the esophagus with extension to the mediastinal nodes so as to form an elongated, stony-hard fixed mass which was obviously inoperable. The wound was closed.

The patient's convalescence was uneventful, and he was discharged at the end of the third week. He died of his disease 3½ months later.

Case 9. M. M., male, aged 60 years, was first seen September 28, 1939, at which time he complained of difficulty in swallowing for the past 4 weeks. At the onset of his illness, dysphagia resulted from ingestion of solid

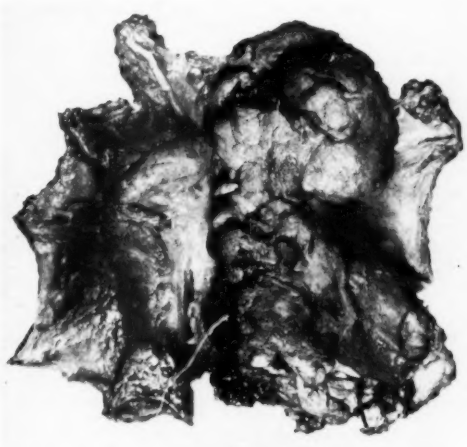

Fig. 10. Case 12. Photograph of operative specimen.

food only, but it rapidly became worse until, at present, he was able to swallow only liquids. At no time had he experienced any pain. The weight loss was 10 pounds. The past, family, and personal history was negative. Examination showed an elderly man in excellent physical condition. Heart and lungs were negative; no enlarged cervical nodes. The abdomen was negative. The prostate gland was moderately enlarged. All laboratory examinations were negative.

The patient was admitted to Mt. Sinai Hospital, where the esophageal roentgenogram disclosed an obstructing neoplasm at the lower end of the esophagus, extending into the cardia of the stomach. Esophagoscopy (Dr. R. Kramer) revealed a granular, ulcerating tumor, beginning at 41 centimeters from the incisor teeth. A biopsy specimen showed adenocarcinoma.

Operation was performed October 6, 1939, under avertin-ethylene anesthesia. The left thoracic cavity was opened through the eighth interspace and the ninth and eighth ribs were divided close to the spine. There was felt a large, firm irregular tumor occupying the terminal 2 inches of the esophagus, with extension into the stomach. Throughout the mediastinum were felt large, hard metastatic lymph nodes which were fixed to the aorta and esophagus. The condition was deemed inoperable and the wound was closed. A small left rectus incision was now made, and a Witzel gastrostomy was performed. Exploration of the upper stomach showed that it was fixed by tumor tissue to the diaphragm and retroperitoneal tissues. The postoperative convalescence was uneventful, and the patient was discharged from the hospital 3 weeks later. He died of his disease soon afterward.

CASE 10. H. Z., male, aged 62 years, was first seen October 9, 1939. He complained of dysphagia of 5 months' duration. This difficulty started rather suddenly, when he noted that swallowed food seemed to stop at a point behind the ensiform cartilage. Dysphagia became progressively worse until he was able to swallow only liquids. One month after the illness began, roentgenological examination was pronounced negative. Esophagoscopy was performed by Dr. John Kernan, September 12, 1939, who found an obstructing, granular tumor, beginning about 40 centimeters from the incisor teeth. A biopsy specimen showed adenocarcinoma. The patient had lost 30 pounds in weight.

Physical examination disclosed a chronically ill man, with obvious weight loss. The left supraclavicular lymph nodes were slightly enlarged. No abdominal masses were palpable. Rectal examination was negative. On the basis of the duration of symptoms, the weight loss, and the origin of the tumor from the cardia, it was felt that the condition was probably inoperable. However, gastrostomy was certainly indicated, and exploration through the abdominal incision could be carried out at the same time.

He was admitted to Mt. Sinai Hospital, where operation was carried out under avertin-ethylene anesthesia. A large carcinoma of the cardia was found extending through the diaphragm into the lower esophagus and infiltrating the under surface of the liver. At the urgent request of the family, gastrostomy was not performed. Convalescence was uneventful, and the patient left the hospital. He died of his disease 10 weeks later.

CASE 11. C. L., male, aged 57 years, was first seen March 1, 1940. He complained of dysphagia of approximately 2 months' duration. This was accompanied by substernal distress. Difficulty in swallowing rapidly became worse until he was able to swallow only liquids. The weight loss was 15 pounds. There was considerable loss of strength but no impairment of appetite. Roentgenographic examination a week before showed an obstructing

Fig. 11. Case 12. Roentgenogram of esophagus and stomach, taken 5 months after operation, showing the wide orifice at the site of anastomosis.

neoplasm in the lower esophagus and cardia, with probable extension toward the fundus of the stomach.

The past history was of considerable interest. Ten years before, he was treated for an ulcer of the lesser curvature of the stomach just below the cardia. The roentgenograms, which had been preserved, clearly indicated the lesion. Under a careful medical regimen, the symptoms abated, with a corresponding roentgenographic disappearance of the ulcer. He was symptom-free until the onset of the present illness.

Physical examination disclosed a chronically ill, moderately anemic elderly man. The cervical nodes were not enlarged. Heart and lungs were negative. No mass was palpable in the abdomen. Rectal examination was negative.

He was admitted to Mt. Sinai Hospital, where esophagoscopy (Dr. R. Kramer) disclosed an obstructing tumor of the esophagus, starting at 39 centimeters from the incisor teeth. A biopsy specimen showed adenocarcinoma. Red blood cell count was 3,300,000; hemoglobin, 70 per cent.

Operation was performed March 7, 1940, under cyclopropane anesthesia. Following a preliminary transfusion, exploration through an upper left rectus incision revealed a large neoplasm of the cardia, adherent to the under surface of the liver, to the aorta, and to the diaphragm. It was obviously inoperable. A Spivack valvular gastrostomy was performed. Convalescence was smooth, and the patient left the hospital 3 weeks later. He died of his disease after 4 months.

CASE 12. S. R., female, aged 58 years, was first seen May 11, 1940. Her main complaint was dysphagia of 6 weeks' duration. About 5 months before, she had had an attack of biliary colic which was followed by anorexia. The onset of dysphagia was not associated with pain or vomiting. Swallowed food seemed to stop at a point behind

Fig. 12. Case 15. Preoperative roentgenogram showing the finger-tip deformity of the cardia and upper fundus.

Fig. 13. Case 15. Photograph of operative specimen.

the ensiform cartilage. There was marked anorexia, and a weight loss of 10 pounds. The patient had suffered from diabetes mellitus for 12 years, and was taking 30 units of insulin daily.

The family history was interesting from the fact that three brothers and two sisters had died of cancer of the breast, liver, stomach, tongue, and stomach, respectively.

Physical examination disclosed an elderly woman, in good general condition. Heart and lungs were negative. Abdominal examination showed enlargement of the liver two fingerbreadths below the costal arch. The edge was sharp and the surface was smooth. No masses were palpable. Lymph nodes were not enlarged. Rectal and pelvic examinations were negative. Roentgenograms submitted by the patient's son, who is a physician, disclosed an irregular stenosing filling defect in the lower esophagus just above the diaphragm (Fig. 9). Laboratory data: red blood cells numbered 5,000,000; hemoglobin, 100 per cent; blood sugar, 135 milligrams per cent; urine, negative.

She was admitted to Mt. Sinai Hospital May 15, 1940. Esophagoscopy (Dr. R. Kramer) showed an ulcerating, stenosing neoplasm, starting at 36 centimeters from the incisor teeth. A biopsy specimen showed adenocarcinoma.

Operation was performed May 21, 1940, under avertin-ethylene anesthesia. In order to determine operability, a small left rectus incision was made. Palpation revealed a neoplasm at the cardiac end of the stomach with extension upward into the esophagus for about 1¼ inches. A few enlarged lymph nodes were felt in the gastrohepatic omentum near the cardia. The liver was normal. The tumor was deemed operable and the wound was closed with through-and-through steel wire sutures. The patient was placed on the right side and the left thoracic cavity opened through the eighth interspace. The eighth, seventh, and sixth ribs were divided close to the spine. The lower 2 inches of esophagus were involved by the new-growth. One enlarged mediastinal node just proximal to this point was removed. The diaphragm was split and the stomach was mobilized by dividing the left gastric and gastroepiploic vessels. The tumor-bearing portion of stomach and esophagus was removed with as much of the gastrohepatic ligament as was feasible. An intrathoracic end-to-side esophagogastrostomy was now performed; two layers of fine silk sutures were used. The stomach was telescoped over the suture line and anchored to the mediastinal pleura and diaphragm. The latter structure was closed about the transplanted stomach. A stab-wound was made in the subjacent intercostal space for an under-water drainage tube, and the operative wound was closed.

During the course of the operation, which consumed 2 hours, a transfusion of 750 cubic centimeters of blood was given. The pulse varied between 90 and 138, and the systolic blood pressure between 148 and 98.

The resected specimen showed an infiltrating adenocarcinoma of the cardiac end of the stomach with involvement of the lower esophagus. Only one node showed metastatic carcinoma (Fig. 10).

The first day after operation the temperature was 102.8 degrees F.; respiration, 24; pulse, 120. Sanguineous fluid discharged through tube. The second day after operation the temperature was 104 degrees F.; respiration, 24 to 32; pulse, 118 to 126. The fourth day, temperature was 101 degrees F.; respiration, 20; pulse, 116. One dram of water was swallowed every half hour without difficulty. Amount of fluid swallowed was rapidly increased thereafter. From the first day, a continuous intravenous drip of 5 per cent glucose in saline was maintained, supported by the necessary amount of insulin. Dr. S. S. Bernstein cared for the diabetic condition. The seventh day, temperature was

100 degrees F.; respiration, 22; pulse, 84. Little discharge came through the chest tube. The operative wounds were clean. All sutures were removed. On the ninth day after operation the chest tube was removed. Temperature was normal, and patient was taking fluids well. On twelfth day phlebitis of left leg with marked edema up to knee was noted. General condition was excellent. Blood sugar was 115 milligrams per cent.

The subsequent course in the hospital was one of continued improvement. The phlebitis subsided completely, and the urine remained sugar-free. The patient was swallowing most foods by the twenty-first day. Upon discharge, June 22, 1940, the hemoglobin was 70 per cent, and the red blood cells numbered 3,800,000.

It is now 5 months since operation. She has regained her lost weight. She swallows all types of food without difficulty and, what is most difficult to explain, she is free of all symptoms of diabetes mellitus and no longer needs insulin (Fig. 11).

CASE 13. H. S., male, aged 67 years, was first seen June 14, 1940, when he complained of dysphagia of 2 months' duration. This was accompanied by lower substernal pain and hiccup. The dysphagia increased slowly until he was able to swallow only liquids. He had lost approximately 5 pounds. He had had lobar pneumonia in 1914, and again in 1920.

Physical examination disclosed an elderly man, weighing 132 pounds, heart and lungs, negative; no enlarged lymph nodes; abdomen, negative. An esophageal roentgenogram showed a small filling defect at the cardia, with marked obstruction in the lower esophagus.

He was admitted to Mt. Sinai Hospital, where esophagoscopy (Dr. R. Kramer) revealed an obstructing, ulcerated neoplasm, beginning at 40 centimeters from the incisor teeth. The biopsy specimen showed an adenocarcinoma. Aside from a mild anemia, all laboratory examinations were negative.

Operation was performed June 28, 1940, under avertin-ethylene anesthesia. Exploration of the upper abdomen through a high left rectus incision revealed the presence of a small neoplasm at the cardia, without palpable enlarged nodes. The tumor was locally operable. However, metastatic nodules were found in the liver, and the abdomen was closed. Convalescence was uneventful, and the patient was discharged. He died of his disease 2 months later.

CASE 14. I. G., female, aged 52 years, was first seen June 22, 1940. She complained of dysphagia of 8 weeks' duration. She noted that swallowed solid food seemed to stop at a point behind the ensiform cartilage and was frequently regurgitated. The dysphagia increased in severity until she was able to swallow only liquids. There was no pain. The weight loss was 10 pounds. The past, personal and family history was negative.

Physical examination disclosed a small, thin, somewhat anemic woman, weighing 90 pounds. The heart and lungs were negative. No abdominal masses were felt. Pelvic and rectal examinations were negative. The esophageal roentgenogram showed a small, irregular filling defect in the lower esophagus just above the diaphragm, with moderate obstruction.

She was admitted to Mt. Sinai Hospital, where further study showed absence of free hydrochloric acid and marked diminution of combined acid in the gastric contents. There was moderate secondary anemia. Esophagoscopy disclosed an obstructing tumor, starting at 38 centimeters from the incisor teeth. The biopsy specimen showed fragments of esophageal wall infiltrated by adenocarcinoma.

Operation was performed June 28, 1940, under avertin-ethylene anesthesia. After a preliminary transfusion, exploration of the upper abdomen through a high left rectus incision revealed a small neoplasm at the cardia which extended upward to involve the terminal portion of the esophagus. Although the tumor was resectable, the finding of metastatic nodules in the liver rendered the condition inoperable. A Janeway gastrostomy was performed. Convalescence was uneventful, and the wound healed by first intention. The patient succumbed 3½ months later.

Fig. 14. Case 15. Roentgenogram of esophagus and stomach showing intrathoracic position of upper stomach and the site of the esophagogastric anastomosis.

CASE 15. A. M., male, aged 60 years, referred by Drs. J. Piller and L. G. Shapiro of Paterson, New Jersey, was seen May 24, 1940. He gave a rather disconnected history, but the essential symptoms were indigestion for 35 years, consisting of epigastric fulness and belching, and midepigastric pain relieved by soda and food. During the past month, epigastric distress had been more or less steady and was more severe after meals. At no time had there been any dysphagia or vomiting. The patient had lost 15 pounds during the preceding year.

Physical examination disclosed an elderly man, in fairly good condition; heart and lungs, negative; no enlarged nodes palpable; abdomen, negative; blood pressure, 118/64. The esophageal and gastric roentgenograms showed a finger-tip defect in the cardia and lower esophagus, with minimal obstruction (Fig. 12).

He was admitted to Mt. Sinai Hospital June 2, 1940. Laboratory tests revealed hemoglobin of 63 per cent; red blood cells, 3,650,000; white blood count, normal; urine, negative; Wassermann, negative. Gastric analysis showed no free hydrochloric acid, a total acid of 50, and a faint trace of blood. Esophagoscopy (Dr. R. Kramer) disclosed a friable ulceration, at 40 centimeters from incisor teeth. Biopsy specimen from edge of ulcer showed adenocarcinoma.

Preoperative preparation consisted of a transfusion of 500 cubic centimeters of whole blood, administration of sulfanilamide, a high caloric liquid intake, the correction of a mild gum infection, and cleansing irrigations of the lower esophagus.

Operation was performed June 6, 1940, under avertin-ethylene anesthesia. Exploration of the upper abdomen was made through a small rectus incision. A tumor was felt at the cardiac orifice, with extension upward into the esophagus. There were no enlarged nodes, and the liver was negative. The wound was closed with through-and-through steel wire sutures. The left thoracic cavity was now opened through the eighth interspace and the eighth, seventh, and sixth ribs were divided close to the spine. The esophagus was exposed and a radial incision was made in the diaphragm. The upper stomach was mobilized by division of the left gastric and gastroepiploic vessels and the tumor-bearing portion of stomach and esophagus was resected (Fig. 13). An intrathoracic end-to-side esophagogastrostomy was then performed, two layers of fine silk being used. The stomach was telescoped over the suture line and anchored to the mediastinal pleura and diaphragm. The phrenic nerve was not disturbed, but large branches of the vagus were sacrificed. An under-water drainage tube was inserted through a stab-wound in the subjacent intercostal space and the wound was closed—time, 2 hours and 5 minutes. During the course of the operation, a transfusion of 500 cubic centimeters was given. The pulse varied between 88 and 136. The systolic blood pressure was fairly steady at 118 millimeters mercury.

On first day after operation temperature was 104.4 degrees F.; pulse, 120; respiration, 26. Nine and one-half ounces of bloody fluid drained from the intercostal tube. On second day, temperature was 103 degrees F.; pulse, 110; respiration, 30. Drainage from tube amounted to 3 ounces. On third day, patient's condition was excellent: temperature, 102 degrees F.; pulse, 98; respiration, 26. On fourth day, temperature was 100 degrees F.; pulse, 104; respiration, 26. Small sips of water were swallowed without difficulty. Thereafter the liquid intake by mouth was rapidly increased. On seventh day, the intercostal tube was removed. The operative wounds healed *per primam*. All sutures were removed.

The patient's convalescence was uneventful. The food intake was increased rapidly. By the eighteenth day, he was swallowing all types of puréed foods and finely ground meats. He was discharged from the hospital on the twenty-third postoperative day.

Now, almost 5 months later, his general condition is excellent. He has gained approximately 15 pounds and eats without difficulty (Fig. 14).

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THE PRIMING ACTION OF STILBESTROL ON THE GRAVID HUMAN UTERUS

A. R. ABARBANEL, M.D., New York, New York

OUR present day knowledge of the combination of circumstances leading to the onset of labor has been logically presented, rationally analyzed, and clearly correlated by Reynolds, who thus summarizes the situation: ". . . there is no known single cause for the onset of labor as the numerous theories of the past and present imply. Rather, it now seems that parturition begins as a result of the gradual accelerating convergence of a number of factors, structural, humoral, nervous, nutritional and circulatory, which, at a time characteristic of each species and adapted to the morphological conditions present in each, are so associated that they lead to evacuation by the uterus of its contents" (11).

Although the exact rôle played by estrogen is still not fully understood, most observers agree that estrogen is the main sensitizing factor for uterine muscle, including that of the human (10, 12). It was on this basis that the use of estrogen was introduced into clinical obstetrical practice by Robinson, Datnow, and Jeffcoate. Using the so called "natural" estrogens (estrone, estradiol, and their benzoic acid esters), these workers reported very encouraging results in the management of missed abortion and labor and of uterine inertia developing during the course of labor. Attempts to induce abortion in the early part of pregnancy (7 to 14 weeks) were uniformly unsuccessful (12). When even relatively huge doses of the natural estrogens were used for the induction of labor, the results were not very encouraging (8, 12, 14).

In a subsequent report Jeffcoate carefully analyzed the possible rôle that estrogen may play, while he further emphasized the excellent results obtained with large amounts of the natural estrogens in the management of uterine inertia and missed labor and abortion (6).

In order to confirm and extend the original observations noted with the natural estrogens, these studies were undertaken (2). The following considerations prompted the choice of the synthetic estrogen, stilbestrol. In the first place, stilbestrol retains most of its potency when administered orally (5). This method of giving the drug thus necessitated a minimum of nursing care, while the patient was not subjected to the discomfort of a series of injections. Second, stilbestrol is not inactivated by the liver (16), while estrone and estradiol are (3, 15). Third, the natural estrogens when given in oil parenterally are slowly absorbed, while stilbestrol is rapidly absorbed from the intestinal tract (4). In summarizing these factors, then, we note that the administration of stilbestrol orally leads to a rapid accumulation of highly active estrogen in the circulating blood.

While these studies were well under way (2), Peel reported that from 10 to 50 milligrams of stilbestrol produced good results in 6 of 13 cases when used for the induction of labor, while, in uterine inertia, success, in whole or in part, was observed in 63 per cent of 11 cases (9). In 3 cases of missed abortion and labor, Peel noted excellent results. Jeffcoate recently extended his observations on the management of missed abortion and labor with estrogens, including stilbestrol, reporting excellent therapeutic response (7).

PROCEDURES AND RESULTS

Twenty-one cases were studied. These were divided into 4 groups: induction of abortion, induction of labor, missed abortion and labor, and uterine inertia. The pertinent data are outlined in Table I.

After various trials, the following routine was finally adopted. Ten to 15 milligrams of stilbestrol was given orally each hour for 10 doses, making a total of 100 to 150 milligrams of stilbestrol administered over a period of 10 hours. From 1 to 8 hours after the last dose of stilbestrol, a routine induction[1] was started. The time interval

From the Department of Obstetrics and Gynecology, Morrisania Hospital, Dr. Harry Aranow, Director.

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[1]The technique of the routine induction used in this clinic is as follows: 6 a.m. castor oil, 2 ounces; 7 a.m., quinine, 10 grains; 8 a.m., hot soap suds enema; 10 a.m., posterior pituitary extract, 3 minims; 10:30 a.m., repeat same dose; 11 a.m., repeat same dose; 11:30 a.m., repeat same dose. If labor does not ensue in 7 hours, the following is done: 7 p.m., hot soap suds enema; 7:30 p.m., posterior pituitary extract, 3 minims; 8 p.m., repeat same dose; 8:30 p.m., repeat same dose, 9 p.m., repeat same dose. As soon as active labor pains begin, the posterior pituitary extract is discontinued. If labor does not begin within 48 hours by this procedure, the induction is considered as unsuccessful.

TABLE I.—RÉSUMÉ OF 21 CASES STUDIED

Group	Case	Age	Para	Pregnant wks.	Indication	Previous inductions	Hrs. labor before stilbestrol	Cervix	Stilbestrol mgm.	Hrs. from first dose of stilbestrol to: Last dose	Start of induction	Onset of labor after	Delivery	Actual labor hrs.	Result	Comment
Induction of abortion	1–5	19–27	4M. 1P.	7–12	Constitutional	0	0	0	100–250	10–66	11–72	No		None	Failure	Uniformly unsuccessful
Induction of labor	6	23	1	42	Post-mature rheumatic heart disease	2	0	0	125	15	16	22 2nd pituitrin	33	11	Success	See text
	7	35	0	37	Large baby, borderline mid pelvis	2	0	0	100	10	11	16½ 3rd pituitrin	29¼	13	Success	Fully dilated in 10 hrs. Midpelvic arrest 3 hrs. Forceps delivery. Baby weighed 8 lbs. 2 oz.
	8	20	0	32	Fulminating pre-eclampsia	1 plus catheters, cervical pack	0		100	10	11	13 Quinine	16¼	3¼	Success	See text
	9	35	5	36	Progressive toxemia	1	0	1cm.	1) 50	5	6	No			Partial success	Insufficient dosage first time? Baby weighed 7 lbs.
								1cm.	2) 150	18	19	21 4th pitocin	34½	13½		
	10	34	2	32	Eclampsia	0	0	0	150	6	7	11¾ 3rd pitocin	14	2¼	Success	See text
	11	20	0	45	Toxemia post-mature	0	0	0	225	50	72	76½ 2nd pituitrin	79½	3	Success	Baby weighed 7 lbs. 1 oz.
	12	33	3	36	Progressive toxemia	0	0	0	100	10	18	27 4th pitocin	35	8	Success	Baby premature
	13	37	0	37	Toxemia	0	0	0	See text						Failure	See text
	14	27	2	32	Fulminating pre-eclampsia	0	0	0	120	12	29	32 Quinine	43	11	Success	Baby weighed 6 lbs. 2 oz.
	15	36	9	36	Pre-eclampsia eclampsia twice before	0	0	0–1 cm.	1) 150	36	48	52 1st pitocin			Partial success	Pains lasted 6 hrs. First time. Second priming 3 days later. Baby weighed 5 lbs. 10 oz.
									2) 150	12	42	47½ 3rd pitocin	48	½		
Missed abortion and labor	16	37	2	25	Fetal death 1 wk.	1	0	0	100	10	22	24 Quinine	61	37	Success	Stenotic cervix
	17	35	9	34	Fetus dead—6 days. Severe toxemia	0	0	0	120	12	26	34½ 4th pitocin	38	3½	Success	See text
	18	32	9	38	Fetus dead—10 days. Severe toxemia	1	0	0–1 cm.	100	36			150	6	Failure	Estrogens alone insufficient, oxytocics also necessary
Uterine inertia	19	42	6	38	Inertia Toxemia	1	36	1–2 cm.	50	5			14½	50¼	Doubtful success	Pains increased in intensity, not frequency. Baby weighed 8 lbs. 8½ oz.
	20	19	0	40	Inertia	1	70	4 cm.	100	10	11	15 1st pituitrin	24	94	Success	See text
	21	39	0	41	Inertia Occiput posterior	1	60	8 cm.	50	2			7	67	Success	Weak pains every 15–30 min. . . . Half hour after 50 mgms. stilbestrol pains strong every 5 min. . . . Forceps delivery. Baby weighed 7 lbs. 13 oz.

intervening before the beginning of the induction was very variable at first, for the effect of the estrogen alone had to be evaluated. In fact, some cases received stilbestrol alone without subsequent medication in order to ascertain if estrogen alone would precipitate the onset of labor. When a routine induction had been previously given, an interval of at least 48 to 72 hours was allowed to elapse before stilbestrol was started. If labor did not ensue after quinine, posterior pituitary extract was given. If pains were transient, the oxytocic was repeated. The maximum number of doses which was used in this series was four, except in the group in which the induction of abortion was attempted.

Induction of abortion. There were 5 cases in this group, 4 being multiparas. They were from 7 to 12 weeks pregnant. A Friedman test in each was positive. The indication for interrupting pregnancy was constitutional, not local, in each instance. Stilbestrol was administered orally in divided amounts, the total dosage ranging from 100 to 250 milligrams over a period of 12 to 72 hours. This was followed by a complete induction including pituitrin, one patient receiving an additional course of ergonovine, 1/320 grain, three times a day for 3 days. In 2, uterine cramps occurred as though menstruation was imminent, after pituitrin was given. In a third patient, slight and transient vaginal spotting resulted. In the primigravida, the nausea that was already present, was aggravated by stilbestrol. This was allayed to a great extent by the simultaneous administration of bile salts (2).

In each case, the attempt to produce an early abortion proved entirely unsuccessful, even though massive doses of stilbestrol, combined with potent oxytocics, were used.

Induction of labor. Ten cases were included in this group. In 7, the indication for terminating pregnancy was a progressive or fulminating toxemia unresponsive to conservative measures. In the 3 others, there was one case each of eclampsia, post maturity associated with rheumatic heart disease, and an elderly primigravida with a large baby and a border line mid-pelvis.

As a rule, the procedure outlined was followed. The exceptions are detailed in Table I. In 2 patients, Cases 6 and 7, 2 previous complete inductions 48 hours apart failed to institute labor. In 2 others, Cases 8 and 9, a previous induction, including the use of extraovular catheters and cervical packing in 1, Case 8, did not precipitate labor. In each of these 4 cases, labor ensued only after first priming with stilbestrol and then using oxytocics. Since the claim might be made that the previous induction had served to sensitize the uterus in some way, the routine induction was omitted in other cases. In some, the toxemia was so severe that it was deemed wiser to help insure a successful induction by first priming with stilbestrol.

In only 1 instance, Case 13, did the uterus fail to respond to oxytocics after the preliminary administration of stilbestrol. The results in the other 9 cases were considered excellent, even though 2, Cases 9 and 15, required a second course of stilbestrol.

The following cases are presented to illustrate the method of approach.

CASE 6. J. B., 118605, aged 23 years, white, secundigravida, primipara, was admitted to the antenatal cardiac ward because of an attack of acute rheumatic fever with cardiac and joint manifestations during her fifth month of gestation. After almost 3 months of bed rest, she was vastly improved clinically except for a mild tachycardia of around 110. She was closely observed until term. After she was past due for 1 week, a medical induction without pituitrin was given with no results. A few days later, a complete induction with pituitrin was given with no effect. Two days later this was repeated with the same negative results. The cervix was still moderately firm and undilated. Three days later, when she was 15 days overdue, she received 25 milligrams of stilbestrol for 3 doses at 7, 8, and 9 p.m. The next morning she received 10 milligrams of stilbestrol every hour for 5 doses, making a total dosage of 125 milligrams. This was followed by a routine induction. After the first dose of pituitrin she began to have irregular contractions which seemed to die out. Five hours later she received a second dose of pituitrin, irregular contractions reappeared, but soon became strong and regular. She delivered spontaneously 6 hours later of a normal female child weighing 9 pounds, 3 ounces (4,167 grams). Total labor, then, counting from the first pain was 11 hours, even though active labor lasted only 6 hours. Lactation set in normally and was fully adequate.

CASE 8. V. G., 116,251, aged 20 years, Porto Rican, secundigravida, nullipara, was admitted to the toxemia ward because of epigastric distress, marked blurring of vision, and ankle edema. Her past history revealed that she had had eclampsia 11 months before.

She was 8 months pregnant. Blood pressure on admission was 215/160. Urinalysis disclosed 4 plus albumin and many hyaline and granular casts. Examination of the eye grounds showed signs of recent hemorrhage, papilledema, cotton wool exudate, and a definite narrowing of the arteries. The fetal heart was regular in rate and rhythm.

A modified Strogonoff regimen was instituted. Blood chemistry studies showed a urea-nitrogen of 34.7, creatinine of 2–0; sugar of 94; uric acid of 8.3. Two rubber catheters were introduced extraovularly, the cervical canal was tightly packed and a routine induction started, pitocin being used. She failed to go into labor. Temperature rose to 102 degrees. At this time the fetal heart sounds disappeared. Two days later, the urea-nitrogen was 53.5; creatinine, 3.1; and uric acid, 8.3. She was then given 10 milligrams of stilbestrol orally every hour for 10 hours, making a total dosage of 100 milligrams. This was followed by castor oil, a hot enema and 10 grains of quinine. Following the latter she went into active labor. In 3 hours and 10 minutes she delivered a stillborn infant. On the next day, the blood chemistry studies revealed essentially no

change, urea-nitrogen being 54.3 and creatinine 3.1. Five days later her uric acid fell to 5.2, creatinine to 2.0, and urea-nitrogen to 42.9. Her postpartum course was very hectic and septic. The cause was finally determined to be malaria, several positive smears being secured.

CASE 10. C.B., 120,130, white, aged 34 years, trigravida, secundipara, was admitted to the toxemia ward at 32 weeks of gestation because of a fulminating toxemia. Two weeks before admission, her blood pressure, which had been normal, rose to 140/90. Since then in spite of careful medical care and strong conservative therapy, her blood pressure steadily increased, and was 220/110 on admission. At this time she complained of marked epigastric distress and persistent pain over the gall bladder region. Edema was 3 plus while urinalysis showed a 4 plus albuminuria with many granular casts. Benzidine test for blood was strongly positive. Ten minutes after admission to the ward, she had an eclamptic convulsion. She was heavily sedated receiving enough morphine to reduce her respiration to 10 to 12 per minute. Blood chemistry studies at this time showed sugar, 87; urea-nitrogen, 44.1; uric acid 9.2; chlorides, 600; total cholesterol, 236; cholesterol esters, 147; creatinine, 2.4; carbon dioxide volumes per cent, 52.7. The fetal heart sounds disappeared 12 hours after admission.

After 24 hours of conservative therapy on a modified Stroganoff regimen, she seemed somewhat better. Since her prognosis was very grave, it was felt best to deliver her as rapidly as possible. Cervix was undilated, moderately firm in consistency. Accordingly, the next morning, she received 25 milligrams of stilbestrol every hour for 6 hours, making a total of 150 milligrams. One hour after the last dose, the routine induction was started, pitocin being used. She went into labor after the third dose and spontaneously delivered a stillborn child 2 hours and 20 minutes later.

The next day her urine showed a 2 plus albumin. Forty-eight hours later just a trace was found. The blood uric acid had fallen to 8.5, the other values remaining unchanged. A week later, uric acid was 3.5; urea-nitrogen, 22.4. The other findings were normal. She was discharged well in 3 weeks.

CASE 13. R. B., 115,161, negress, aged 37 years, secundigravida, nullipara, was admitted to the hospital for observation because of a sudden rise in blood pressure to 160/90 and 1 plus albuminuria which developed during antisyphilitic therapy with neoarsphenamine. She was 34 weeks pregnant. On conservative therapy she improved. When she was 37 weeks pregnant the following observations were recorded. Cervix was long, firm, undilated. She received 50 milligrams of stilbestrol daily in 10 milligram doses for 3 days, making a total dosage of 150 milligrams. Labor did not ensue. On the fourth day she received a routine induction. After the third dose of pituitrin she began to have active pains. These lasted for 5 hours, then died out.

During the course of the next 2 days she received 110 milligrams of stilbestrol followed by another routine induction. After the third dose of pituitrin, she began to have active pains. These lasted for only 6 hours.

After a 24 hour rest, at the suggestion of Dr. Leo Wilson, she received 100 milligrams of anhydro-oxy-progesterone for 3 days, making a total dosage of 300 milligrams. Labor did not ensue. On the fourth day, after she had received 2 doses of pituitrin, she apparently had a few mild contractions during the course of an hour.

Two days later it was decided to combine stilbestrol and anhydro-oxy-progesterone. Accordingly, she received 50 milligrams of stilbestrol during the course of one day, 100 milligrams of pregneninolone on the second day, and a routine induction on the third day. After the third dose of pituitrin she had strong pains which lasted for one hour.

Three days later, she had a normal spontaneous delivery after a total labor of 6½ hours. The baby weighed 7 pounds, 2 ounces (3,230 grams). Furthermore, lactation was normal.

Missed abortion and labor. There were 3 cases in this group, 2 of missed labor associated with progressive toxemia and the third a case of missed abortion. (Cases 16, 17, 18.) Results were excellent in Cases 16 and 17. In Case 18, one of missed labor, stilbestrol alone, given without subsequent oxytocics, was without effect. The results obtained in this group are similar to the ones secured with the natural estrogens (6, 12) and stilbestrol (7, 9).

The following case indicates the successful priming action of stilbestrol in an instance of missed labor.

CASE 17. G.M., 114,436, aged 35 years, decigravida, nonipara, was admitted to the toxemia ward 6 weeks before term because her blood pressure had risen to 176/104 while urinalysis revealed a 4 plus albuminuria and occasional casts. The patient complained of marked nausea, vomiting, and severe headaches. She had not felt "life" for over a week. Blood chemistry studies were within normal limits except for a serum protein of 4.93. Peripheral edema was marked. Fetal heart sounds were not heard.

On conservative therapy she failed to respond. It was felt that evacuation of the uterus was imperative. Cervix was fairly firm, and was a finger tip dilated. Accordingly, she received 10 milligrams of stilbestrol every hour for 12 doses, making a total dosage of 120 milligrams of stilbestrol. She failed to go into labor in 14 hours. A routine induction was then started. After the fourth dose of pitocin, she went into active labor, delivering a stillborn macerated fetus 3 hours and 25 minutes later.

Uterine inertia. Three cases of uterine inertia were studied. The result in 2, Cases 20 and 21, was considered successful. In the third, Case 19, the result was good, but was classified as doubtful for the pains increased in intensity but not in frequency. The results obtained compare favorably with those secured with the natural estrogens (6, 12) and with stilbestrol (9).

The following case is presented in detail to illustrate the method of approach.

CASE 20. (The author is indebted to Dr. Ramon Basora for the details of this case.) E.S., white, aged 19 years, secundigravida, nullipara, 1 miscarriage. Pregnancy was uneventful until her blood pressure rose to 140/90 2 days after her expected date of confinement. Pelvis was adequate. She was given a routine induction following which she went into labor, pains occurring at 15 to 20 minute intervals, being weak in intensity. These continued for 2 days the cervix dilating to 3 to 4 centimeters. Pains then died out. The next morning she was given 10 milligrams of stilbestrol every hour for 10 doses making a total dosage of 100 milligrams. Another induction was started and after the first dose of pituitrin she went into very active labor and was delivered of a normal female child by prophylactic low forceps a little less than 9 hours later.

ANALYSIS OF RESULTS

The results obtained in cases of uterine inertia and missed abortion and labor are similar to those reported elsewhere both for the natural estrogens and for stilbestrol. Attempts to induce abortion with stilbestrol in the early part of pregnancy were as uniformly unsuccessful as those noted with natural estrogens. Why the uterus should fail to respond in the early weeks of pregnancy still is beyond the ken of our present day knowledge.

After the first half of gestation, however, the uterus apparently becomes responsive to potent oxytocics after preliminary priming with sufficient amounts of estrogen. To this may be ascribed the favorable results secured in the induction of labor. The results obtained with stilbestrol, moreover, seem to be somewhat better than those obtained with the so called natural estrogens—estradiol and estrone (8, 12, 14). In discussing the use of estradiol and estrone for the induction of labor, Robinson, Datnow, and Jeffcoate stated that the administration of these estrogens near term may bring on labor, but was not reliable, whereas for cases where rapid delivery was essential, estrogen was unsuitable (3). These statements must be qualified by the following considerations. In the first place, the natural estrogens were administered parenterally in oil, a factor hindering rapid absorption. Second, the natural estrogens are inactivated by the liver (3, 15), while stilbestrol is not (16). Moreover, stilbestrol is readily absorbed from the intestinal tract. In short, the metabolism of stilbestrol is such that a high concentration of active estrogen in the circulating blood is rapidly attained. By using large doses over a relatively short period of time, a successful therapeutic result is further ensured. The results obtained in this series appear to offer valid evidence supporting these statements.

Analysis of the data in Table I apparently demonstrates that the estrogen, stilbestrol, alone, regardless of dosage (up to 225 mgms.) or time (3 days), did not initiate labor. Furthermore, in 4 patients one or more inductions, including the use of potent oxytocic posterior pituitary extracts, had been unsuccessful. In short, the use of estrogen alone or the use of oxytocics alone, was insufficient. It was only when estrogen was used in sufficient dosage to sensitize the uterus to the subsequent action of oxytocics that labor ensued. Moreover, it should be noted that labor practically always set in within a very short time after the administration of oxytocics was begun. This phenomenon might be called a one-two reaction (estrogen-oxytocic).

All in all, these data seem to show that a successful and rapid induction of labor in the last trimester of pregnancy may be insured by the preliminary priming of the uterus with 100 to 150 milligrams of oral stilbestrol to the subsequent action of potent oxytocics.

A word may be said about the so called "toxic" effects of stilbestrol noted especially in the menopausal patient (13). The most frequent side effect seemed to be nausea and vomiting. Previous studies in this clinic had demonstrated that the puerperal patient could easily ingest from 250 milligrams of stilbestrol daily to 1500 milligrams weekly (1). Careful blood and urine studies had failed to disclose any so called "toxic" effects. Consequently, it was felt that stilbestrol was a safe substance to administer to the pregnant patient, even though evident cardiovascular, renal or hepatic damage might be present. In 15 of the cases in this series, some evidence of toxemia was found, yet no harmful effects could be ascertained even by extremely critical observers. Two patients experienced mild nausea, which was relieved by bile salts. A third one, who vomited after a meal containing cabbage, experienced no difficulty whatsoever 2 days later when she received a similar amount of stilbestrol.

The duration of labor in the successful cases seemed, as a rule, to be somewhat less than normal. It should be noted that the duration of labor has been calculated from the time of the first pain, not from the time pains become strong and regular. In the vast majority the labor progressed very smoothly. No adverse effects were noted in the third stage of labor either with separation of the placenta or postpartum bleeding. Careful pediatric check up failed to note any effects upon the babies.

There was one case of puerperal morbidity, Case 8, which was found to be caused by malaria. In those mothers who nursed their babies no ill effect was observed upon subsequent lactation. The initiation of milk secretion was not delayed (1). In the toxemia patients the elevated blood pressure seemed to be unaffected by stilbestrol.

SUMMARY

1. Attempts to induce early abortion with stilbestrol were uniformly unsuccessful in 5 cases. Stilbestrol in dosages from 100 to 250 milligrams orally failed to prime the gravid uterus of the first trimester of pregnancy to the subsequent action of potent oxytocics.

2. For the induction of labor in the last trimester of pregnancy, stilbestrol, in oral dosages averaging 100 to 150 milligrams, appeared to be

an excellent priming agent for the subsequent action of oxytocics on the gravid uterus. The result was considered successful in 9 cases, 90 per cent, although in 2 of these a second priming with stilbestrol was necessary. Stilbestrol alone was ineffectual. It was only when this estrogen was followed by the use of potent oxytocics that labor ensued. These results are merely suggestive and far from conclusive.

3. In one case of missed abortion and one of missed labor, stilbestrol successfully primed the uterus to the subsequent action of oxytocics. In a second case of missed labor, the use of stilbestrol alone, without being followed by oxytocics, proved unsuccessful in precipitating labor.

4. In 3 instances of uterine inertia, a good result was apparently secured in 2, while in the third, the effectiveness of stilbestrol *per se* seemed questionable, even though the result appeared to be good.

5. The pregnant patient, especially in the last trimester of pregnancy, is very tolerant of large doses of oral stilbestrol, even though severe grades of toxemia may be present.

6. No adverse effects were observed upon the third stage of labor, the babies, the postpartum morbidity, the lochia, or upon the subsequent lactation.

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THE EFFECT OF COOLING TRAUMATIZED AND POTENTIALLY INFECTED LIMBS

ROBERT T. McELVENNY, M.D., Oak Park, Illinois

FOR centuries the beneficial effects of heat and cold in the treatment of infection has been appreciated. But as Brooks and Duncan have pointed out, the outstanding fact is the paucity of investigative knowledge relative to the effects of heat and cold on tissue.

Allen has done both experimental and clinical study on the effect of cooling limbs rendered ischemic by tourniquet, by ligating great vessels, or by vascular accident. Allen states: "Theoretically, at least, the following possible uses of cooling an extremity may be suggested."

1. In embolectomy. With prompt cooling of limbs the time limit in which embolectomy can be performed can be lengthened beyond 4 hours. Allen bases this statement on the fact that he has shown experimentally that cooling limbs subjected to local asphyxia by tourniquet or by ligating great vessels greatly prolongs the time a tourniquet can be left on a limb with resultant recovery when the constrictor is removed.

2. In diabetic and arteriosclerotic gangrene.

3. In emergency surgery. "Theoretically this plan of cooling a limb and applying a tourniquet can be recommended more positively for emergency purposes. Occasionally there are accidents in isolated localities and on a larger scale there are military emergencies when anesthetics may be lacking or surgical care may be delayed. If ice is available the tourniquet and refrigeration can be applied by anybody of reasonable intelligence. Hemorrhage and pain are thus stopped and both local tissue damage and the systemic shock which prolonged ligation at ordinary temperatures produces are abolished. Theoretically a limb might be preserved in ice or ice water for twenty-four hours or more if the ligation is not too high but it is safer to limit the time to five or six hours." This statement refers to limbs in which survival of the part is to be sought.

I first became acquainted with the application of Allen's work about 18 months ago when I had an opportunity to observe the work being done on the Fifth Surgical Service at the Boston City Hospital. At that time the following method of treating gangrene of the foot in the elderly or poor risk patient was started:

From the West Suburban Hospital, Oak Park.

The limb was surrounded with shaved ice up to the elected site of proposed amputation in the thigh. Soon after icing, all pain would disappear from the limb. Twenty-four hours after the application of the ice, a tourniquet would be placed tightly about the thigh just below the site of proposed amputation. Because absorption of toxins was prevented by this treatment, the patient would begin to improve. In 4 to 5 days his condition would be such that amputation could be done. The tourniquet would then be removed and the amputation would be done through the tourniquet site with no anesthetic except that provided by the pressure produced by the tourniquet. I watched an amputation in one of these cases and it appeared to be absolutely painless and was practically bloodless.

Allen (1) states: "The only right way to present a new practical proposal is on the basis of a sufficient series of case records for demonstration, and the lack of such is regretted. A possible use of refrigeration in nondiabetic surgery for reducing shock in extensive injuries and operations involving the lower limbs and pelvis must also be left as a mere theoretical suggestion."

The following case is presented because it is believed that beneficial effects, both general and local, were obtained by the application of Allen's principles to a severe traumatic injury; also to bring forth the fact that cooling was used not to preserve a portion of a limb but to prevent the development and progress of bacterial infection and invasion in heavily contaminated and potentially infected wounds.

The morning of November 30, 1940, I was called to see a man aged 50 years, who 1 hour previously had been run over by a railroad train which had amputated his left leg just above the knee and his right leg through the knee joint. The man was lying on the floor of the emergency room when I first saw him.

The house surgeon had applied tourniquets about the thighs. The man was bled out and was in profound shock. His blood pressure was 30/0. He was receiving 1500 cubic centimeters of gum acacia through the veins of both arms. As soon as possible whole blood was given because it was felt it would be more beneficial than blood serum. The tourniquets were released and all bleeding points were seized with hemostats which were left in place. The tourniquets were left around the thighs in case they were needed. The stumps were wrapped in gauze soaked in a solution of sulfanilamide.

Two hours later the patient's blood pressure was 40/0. Eight hours after injury his blood pressure was 50/10.

The day of the accident was slushy and because of the sudden application of the train's brakes, the undercarriage of the cars had rained snow, mud, and sand over the limbs. This material was ground up and mixed with clothing, huge flaps of skin, muscle, and bone. The ends of the stumps were ragged and extensively macerated.

Ten hours after injury the patient complained of pain in the left chest. He was irrational and was tossing from side to side complaining of pain in his feet and legs. An electrocardiogram showed sinus tachycardia. His blood pressure remained about the same.

Twenty hours after injury a pronounced foul odor was emanating from the stumps. Large doses of morphine were needed to control him. He was coughing. He was irrational. His blood pressure had shown no rise. A consultant confirmed the diagnosis of pneumonia and sulfapyridine was substituted for the sulfanilamide he had been getting. He still received neoprontosil. His temperature was 101.4 degrees by axilla.

It was evident that nothing at this time could be done for the patient's lower extremities. The gauze was removed from the stumps and they were completely enclosed in shaved ice to 2 inches above the extent of tissue damage. No tourniquets were applied. Within 1 hour following the application of the ice all pain ceased in the lower limbs. Soon the foul odor from the stumps vanished. The patient soon became quite rational and it was possible to take his temperature by mouth. The icing profoundly affected his temperature because it fell to 97.2 degrees by mouth. Heat blankets were applied over the patient's body and his temperature again rose to around 101.0 degrees by mouth. Supportive treatment was given including blood. He was given three successive prophylactic doses of combined sera.

On Monday afternoon, December 2, 58 hours after injury the patient's condition had markedly improved. Blood pressure was 110/60. Fever was 101 degrees by mouth. The pneumonia was not progressing. At this time the patient was taken to the operating room and under ethylene anesthesia both lower extremities were elevated, high tourniquets were applied, and a simultaneous bilateral amputation was done. On the left side the site was through the mid-thigh and on the right side the site was through the lower third of the thigh. A 'fish-mouth' type of incision was used. The muscle jumped and retracted smartly. The flaps were allowed to fall together. Soft rubber drains were inserted and a few loose silkworm sutures were used to gently approximate the flaps. There was no redness, induration, or ecchymosis of either thigh at or below the site of amputation. During operation his blood pressure fell from 110 to 105. He was transfused on the operating table.

The day following operation the patient broke into a profuse sweat. His fever dropped by crisis to normal. His chest condition rapidly resolved. Since that time the patient's recovery has been uneventful. His fever never exceeded 100 degrees by mouth and after the sixth postoperative day it has been normal. Five days after surgery the patient was sitting up in bed reading a paper and smoking his pipe. The stumps were healing kindly with no signs of induration, infection, or slough of skin or other tissue. Drainage from both stumps was diminishing and at the end of 6 weeks both stumps were practically healed.

The appearance of the amputated parts was interesting. They were cold and firm. There was no gross evidence of infection or inflammation. The muscle was red and healthy looking. The fascia glistened. There were no blood clots. This was probably due to the washing achieved by the melting ice. The blood was red and fresh looking. The mud and sand were moist and looked as of the day of the accident. The particles of sand stood out in bold relief on the surface of the tissue with no signs of sticking to the tissue as is so often seen in wounds that are softened by disintegration of tissue. The subcutaneous fat was firm. There was no odor except from a few soft, bluish white tags of skin which had not been included in the ice.

A case has been presented of traumatic amputation in which ice was used to surround the members in order to prevent the advance of bacterial infection. The purpose of this was to obtain time in which the patient's general condition could be improved sufficiently to permit major surgery. In this case 58 hours elapsed between the time of accident and the surgical amputation of both limbs through the thigh.

This case does not permit one to say whether the oral sulfapyridine, the intramuscular neoprontosil, the local sulfanilamide, or the local icing was the determining factor in the result. The lack of cultures taken from the wounds limits effective discussion. It would seem, however, that icing did stop local pain, did materially aid the patient in combating shock, and did stop all odors emanating from the stumps. The patient's improvement was remarkable following the application of the ice. The pieces of skin not included in the ice were gangrenous while equally detached pieces of skin that were included in the ice were well preserved. Physiologically and bacteriologically the procedure would seem to be sound.

If upon continued investigation these findings are confirmed, the method advocated by Allen of cooling limbs might find wide application in severe wounds in both civil and military life. This cooling might be effected by ice or gas. It would be of use not only in extremities that might be saved but it would be of value in holding infection in abeyance in hopelessly traumatized limbs or parts in those cases in which surgical aid is not immediately forthcoming either because of the patient or because of the circumstances under which the accident occurred.

Undoubtedly ice has been used for the purpose reported here but the writer was unable to find reference to any such case. With this in mind it is hoped others will try the method to see if the principles advocated by Allen and applied here are substantiated by extensive clinical experience.

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AUGUST, 1941

THICK SPLIT SKIN GRAFTS IN THE REPAIR OF BURNS

WHEN the full thickness of the skin is destroyed by a burn over a large area, an open wound results, and, unless there is early replacement of the lost skin, healing will occur by contracture of adjacent tissue and by "scar" epithelium, or permanent healing may never occur.

Almost any treatment that promises as little work as possible is apt to become popular; but, so far, no application has been found that will produce normal skin and, when it is claimed that a certain preparation will insure complete healing without scarring, it apparently is not realized how healing occurs in superficial and in full thickness losses of skin.

If there is rapid healing and return to function following a burn without much scarring or deformity, this simply means that the full thickness of the skin has not been lost, and that regeneration has occurred from the deep glands in the derma, much the same as occurs in the donor site of a thick split graft.

It has been observed that these struggling cells are easily killed by chemical, bacterial, or mechanical trauma. Therefore, it appears that cleanliness, protection, and the avoidance of strong chemicals will best promote this type of healing, and these objects of treatment seem to have stood the test of time.

The local care of open wounds has for its object the cleaning up of the areas as quickly as possible, so that the lost surface may be restored with skin grafts before contractures have occurred and before debilitation and pain have developed beyond control. Soap and water cleansing and surgical drainage accomplished by saline dressings or saline baths usually suffice, but antiseptics, Dakin's solution, or sulfanilamide may be thought necessary.

A fundamental of dressing all raw wounds is that old linen, or very fine mesh gauze be placed next to the surface so that granulations will not grow up through the coarse meshes of overlying gauze, stick, and cause pain. When cellulitis is controlled, grease dressings on fine gauze or linen can be used.

A firm pressure or elastic dressing may be of great advantage, and discolored, edematous granulations may be flattened out into a firm, bright red surface without chemicals or without cutting them away.

The continual saline bath may have the important result that most secondary contractures will be straightened out by the voluntary effort of the patient without the use of traction or restraints. Many patients are extremely grateful for the bath and realize their first comfort in it, and it has occasionally been a life-saving measure. If there is any unfavorable reaction to the bath, it is omitted.

It seems impossible to sterilize large open areas, but careful evaluation of the general condition and of the gross appearance of the granulations and surrounding tissues usually suffices for the determination of the time for operation, and many deep burns are ready for grafting in 3 weeks' time.

The general condition of the patient is directly reflected in the wounds and, of course, should be considered primarily in all instances. Gentleness in all manipulations is always an essential of care.

A graft of from one-half to three-fourths of the thickness of the whole skin is perhaps the most useful in making repairs of raw surfaces. This could be designated as a "thick Ollier-Thiersch" or as a "thick split-graft." (The original Ollier-Thiersch graft was described as being cut just through the papillary layer of the epidermis which makes it very thin without any derma; however, the thin pad of derma happens to be a most important part of a skin graft.)

When large areas are to be covered, it is necessary to obtain large thick grafts without cutting entirely through the derma so that healing of the donor site can occur rapidly without leaving any further defect. The deep glands left behind in the derma of the donor site "de-differentiate" into squamous epithelium and cover the surface in from six to eight days. This can be shown microscopically and is a very interesting study in wound healing, and might be considered as a reverse of the process of carcinoma formation. As many as five "crops" of skin have been cut from the same area and as little as nineteen days have been required for the production of a new surface suitable to supply another crop. There must be careful protection of the donor sites.

The most necessary equipment in obtaining split skin grafts is a very sharp, long knife of the amputation variety. Large grafts may be cut rapidly, and the larger they are the more easily they may be applied; grafts up to eighteen by five inches may be obtained from suitable thighs. With some practice the thickness can be easily graduated with free hand-cutting; one should realize that the thickness of the graft should depend on the relative full thickness of the skin of the area. This thickness varies greatly in different parts of the body and in different patients, so that a set thickness cannot be described for this graft. The essential is that it be cut thick but not too thick to prevent the donor site from healing promptly.

With mechanical aids such as the dermatome, the suction retractor, or by elevation of the skin with large tenacula, fairly large grafts may be cut even from the abdomen. But patented equipment does not cut the graft and care has to be exercised in their use not to cut through the derma.

These grafts are applied to the prepared area, and held at about normal skin tension with No. 000 silk sutures all around and with multiple mattressing sutures over the surface. In suitable areas the grafts may be spread out and then "snubbed" in place with a sterile fine mesh roller bandage.

Either saline or grease fine mesh gauze dressings are used according to the degree of contamination thought to be present, and pressure is obtained over the area with mechanic's cotton waste or marine sponges bound on firmly with heavy gauze rolls. The application of pressure to the dressings is a fundamental as important as any other operative step.

Many methods of cutting split grafts have been described and different terms applied to the graft. If the full thickness of the skin is not taken, then the skin necessarily has been split in two and the graft is at least anatomically a "split" graft. To have a new type of

skin graft would require a new type of skin, but, as new authors realize how utilizable the split graft really is, enthusiastic reports are made with new terminology.

Full thickness grafts are not put over large raw surfaces because the size required is prohibitive, and the take of a full thickness dissected graft is not as certain in contaminated fields as that of the split graft. This graft is used extensively in healed deformities in which a clean operation can be done, mainly on exposed surfaces, and the healing seems to give a better chance of immediate return of the area to normal. Even in these grafts, pigmentation may be troublesome and require the use of cosmetics.

There is a large field of usefulness involved in this work and large room for improvement, such as simplification of effort, study of the effect of local refrigeration, and the possibility of getting the homografts to survive. At the present time, with careful removal of the grafts so that prompt healing of the donor site occurs, most patients can supply enough skin for their repair. As many as five crops have been taken from the same area, 220 square inches have been transferred at one time and a total of 600 square inches has been grafted in a single patient. The laborious use of full thickness grafts and more tedious use of pedicle flaps in many instances can be avoided.

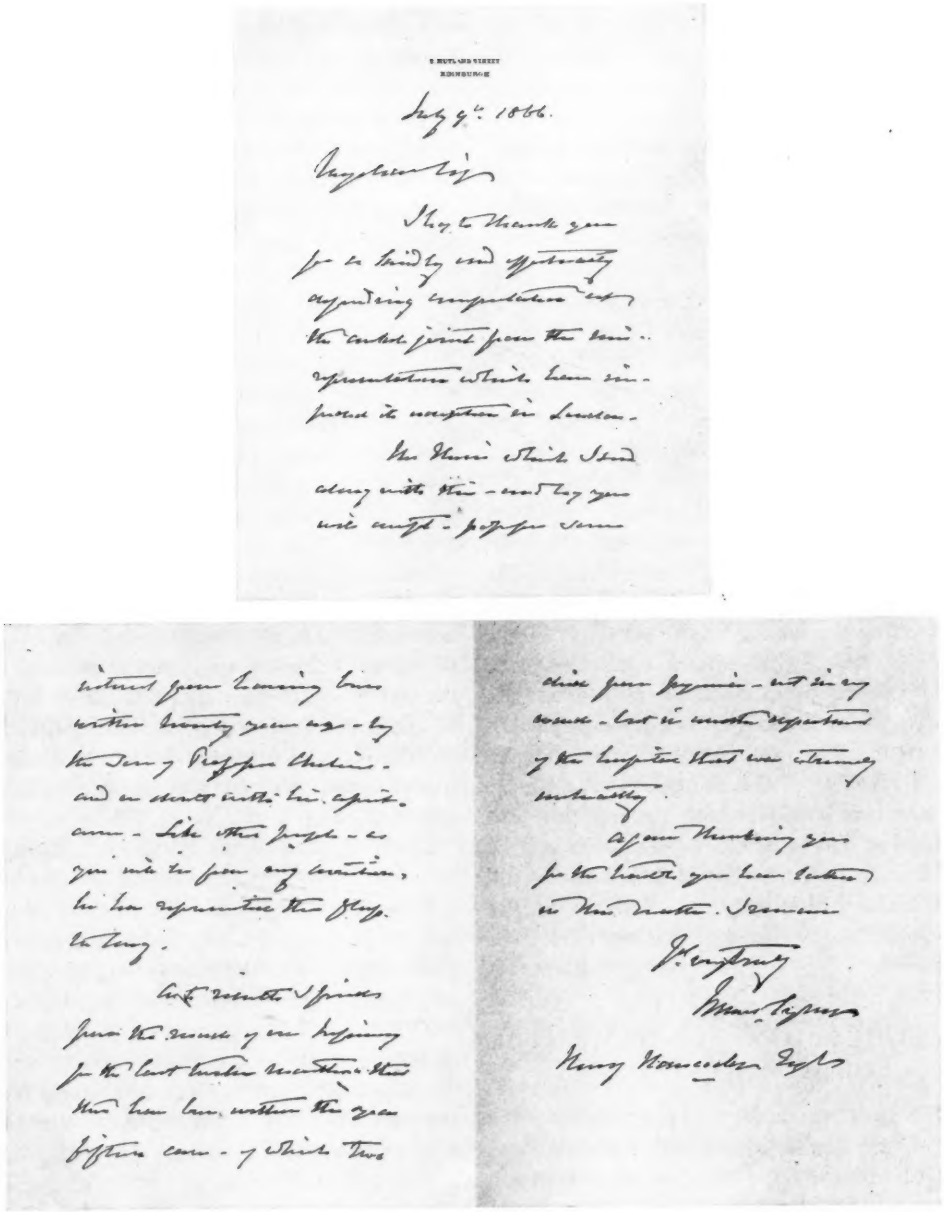
JAMES BARRETT BROWN.

A FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

IN the program for the next meeting of the American College of Surgeons at Boston, November 3 to 7, 1941, an experiment will be tried. On three mornings a series of brief presentations of advances in surgery will be made by representatives of various university departments of surgery. In general the representatives will be the younger men, many of them too young to fulfill the age requirement for fellowship in the College. This innovation in its program will be under the direction of Dr. Owen H. Wangensteen of the University of Minnesota.

The College recognizes a need long felt by many to give those beginning productive careers in surgery an opportunity to present the results of their own research activities. Although it is generally realized, as Osler pointed out long ago, that the most important original work is the product of the young man, but little opportunity has been given him to present his ideas and work before the representative surgical bodies of this country. In the national societies one of the requirements for fellowship is that the candidate have reached a certain age before he can become a member or appear on the program of the Society. Somewhat in protest against the restrictions placed upon the younger, productive surgeon, the last two years have witnessed the creation of two new organizations which are primarily for the younger men: the Society of University Surgeons and the Central Surgical Association.

In the creation of the forum on fundamental surgical problems the College believes that a dual opportunity is afforded to carry out its original purpose; it is hoped that this innovation will not only fulfill the need of giving the younger surgical investigators an audience but that it will also serve as a means of acquainting the older surgeons with the newer developments. Surgery has moved on from the time when it was based only on anatomy and pathology. Physiology, chemistry and physics are now important sources of inspiration for it. If he wishes to be in the forefront of his profession, the modern surgeon must be versed in the applications of what may seem to be only distantly related sciences.



Facsimile of a letter of James Symes, Scotch surgeon known for his description of an operation for amputation at the ankle joint.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE general pattern of the first edition in 1918 is followed in the ninth edition of Macleod's *Physiology and Biochemistry in Modern Medicine.*[1] In later editions the proportion of biochemistry was reduced and the title was correspondingly changed. The first edition was mainly the work of the late J. J. R. Macleod; the present edition is the work of Bard, as editor and part author, and of nine collaborating specialists.

The intention has been to treat a wide range of topics in physiology in a fundamental, detailed, and critical way: to avoid, on the one hand, the historical approach, exposition of laboratory method, and compact treatment desirable in an introductory textbook and, on the other hand, the "predigested knowledge suitable for immediate bedside application" desirable in practical work for quick reference. The book is not intended as a survey for beginners, nor does it set out to cover all aspects and divisions of human physiology. The outstanding omission, as in former editions, is the physical physiology of reproduction; by a paradox the authors include the chemical aspects of this subject.

The book should be extremely valuable to anyone who undertakes laboratory or clinical research on problems presenting physiological aspects. Its value from this standpoint is enhanced by a remarkable bibliography of more than 2200 references, an excellent key for existing physiological literature. It will also make useful collateral reading for medical students and will interest physicians endeavoring to keep up with the times. FREDERIC T. JUNG.

THE fact that the splendid volume, *Anus, Rectum, Sigmoid Colon* by Bacon,[2] appears in a second edition so soon after its initial publication (17 months) speaks for its wide and ready acceptance by those who are interested in proctology. The book is definitely encyclopedic in form, encompassing as it does the entire field of rectal surgery and allied subjects. There is an outline preceding and a most complete and up-to-date bibliography following each chapter. The work is well organized for quick reference.

Surgical anatomy, methods of examination, aids in diagnosis, anesthesia, and analgesia are taken up in the first 100 pages. In the remaining 747 pages, the author presents a systematic and thorough discussion of all the pathological processes affecting the perianal area, anus, rectum, and sigmoid colon. The so called minor rectal ailments receive as much attention as do the major problems.

Detailed step by step directions are given for the treatment of such common anal conditions as fissure, cryptitis, hemorrhoids, abscess, fistula, and pruritis ani. Nearly a third of the book is devoted to benign and malignant tumors of the rectum. The surgical technique of Miles, Gabriel, Jones, Lahey, Rankin, Lockhart-Mummery, Babcock, Coffey, Bickham, and Mikulicz are described and the applicability of each to the various types and locations of rectal carcinoma is given.

This second edition includes new operative procedures for rectal prolapse and hemorrhoids, together with various means of avoiding postoperative pain. There is a description of Devine's defunctioning colostomy. Included is a discussion of the author's recent work on extrarectal metastatic growths from upper abdominal malignancy, which are often mistaken for primary rectal carcinoma. The surgical treatment of supralevator abscess, both of the retrorectal and pelvirectal fossae, is given. The treatment of chronic ulcerative proctosigmoiditis and the sequelae of lymphogranuloma inguinale with sulfanilamide is described.

In order to ease the reader in the selection of the procedure of choice, summaries of treatment have been placed at the end of many chapters.

Four hundred eighty-seven illustrations and clinical photographs, as well as numerous "differential diagnosis charts," are used to enhance the work, and are uniformly good.

The book is written in a concise, direct, and readable manner. It is highly recommended as a guide for the general practitioner or surgeon and as a book of reference for the specialist.

THOMAS J. MERAR.

THE 910 page book *Emergency Surgery* by Hamilton Bailey[3] contains some 930 illustrations, many in color. It covers in encyclopedic style most of the surgical conditions which may be considered as emergencies as well as many which can hardly be classed as such. The book has all of the advantages to be gained from a personalized style of presentation.

Although of value to the surgeon of broad experience its chief use will be that of a handy reference for the occasional operator confronted with an emergency case. Like all textbooks it is somewhat

[1] MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE. Edited by Philip Bard, et al. 9th ed. St. Louis: The C. V. Mosby Co., 1941.

[2] ANUS, RECTUM, SIGMOID COLON; DIAGNOSIS AND TREATMENT. By Harry Ellicott Bacon, B.S., M.D., F.A.C.S., F.A.P.S. Philadelphia, Montreal, and London: J. B. Lippincott Co., 1941.

[3] EMERGENCY SURGERY. By Hamilton Bailey, F.R.C.S. (Eng.). 4th ed. Baltimore: The Williams & Wilkins Co., 1940.

out of date by the time it reaches the press. The small amount of space devoted to the use of heparin in vascular surgery is an example of this type of defect. THOMAS DOUGLASS.

THIS year marks the fortieth anniversary of the Year Book series and the ninth of the *Year Book of Radiology*.[1] The editors have co-operated in celebrating this anniversary year by contributing previously unpublished papers on subjects with which they have been prominently identified. Dr. Waters' paper deals with preoperative irradiation of renal tumors while Dr. Kaplan reports on his rich experience with the treatment of amenorrhea and sterility. A very readable preface, "The Story of the Year Book of Radiology" by the publishers, adds considerable interest to the volume.

As in previous years this edition covers the progress of radiology during the past year in a concise yet adequate manner. The selection of the material to be reviewed by the editors reflects the value of their wide experience and sound judgment. It is of interest to note that there has not been such a marked decrease in available contributions from abroad as might be expected. Whereas the diagnostic section of the 1939 edition consisted of approximately 45 per cent of foreign articles, in this edition slightly less than 35 per cent of the material came from foreign sources. Dr. Kaplan, however, mentions the effect of the international situation as reflected by the value of the articles dealing with radiotherapeutics published abroad. The safeguarding of radium in the countries at war has become a problem. Provisions have been made in some countries for underground storage to prevent loss and scattering of radium following explosive destruction.

A review of this edition impresses one with the continued growth and expansion of the science of radiology. It would be superfluous to attempt to select particular papers as outstanding. Every page contains items of interest and importance. The *Year Book of Radiology* has proved its value during the past years. The same excellent qualities are preserved in this edition. The reviewer finds it indispensable in his work and ventures to say that this is the feeling of the great majority of radiologists. It is recommended without reservation not only to the radiologist but to any physician who is interested in acquainting himself with the recent advances in radiologic diagnosis and radiotherapeutics.

EARL E. BARTH.

THAT wound surgery is simply good surgery is brought out significantly in Bailey's introduction to *Surgery of Modern Warfare*,[2] with the observation that if the only message conveyed by the book were to make the distinction clear between wound excision and débridement, the volume "would be worthy of study by the war surgeons." About this distinction between wound excision and débridement can be written the whole rationale of the local treatment of wounds.

The material contained in the volume at hand is divided into 8 sections and 54 chapters. The first two sections, or a slight one-third of the book, is given over to a consideration of wounds in general, while the remainder of the book is devoted to the consideration of wounds as they affect the various regions of the body. No less than sixty-five surgeons and other specialists have contributed, and from this authoritative and succinct compilation, ably edited by Hamilton Bailey, may be obtained the best picture of war surgery today. Written possibly somewhat hurriedly and under stress of disruptions, this may serve rather as commendation than as adverse criticism since the contributors have daily forced upon them the importance of their observations and the necessity of brevity of expression. Repetitions and inconsistencies in the presentation of material will doubtless be ironed out in subsequent issues and are not to be considered entirely a fault since they represent the diversity of opinions which make surgery a growing science.

Wounds in warfare are considered in relation to the agents causing them, in order that proper appreciation of the possible extent of damage may be obtained. Surgeons with experience in the war of 1914–18 are already familiar with the action of various types of bullet and shell fragment injuries and the extensive disruptive and concussion effects of modern high velocity missiles which may extend far beyond the area of apparent damage. The effect of the aerial bomb, however, has not been so well known and experiences with these wounds are particularly illuminating.

A brief discussion of current concepts of the causes and management of shock is followed by a lengthier discussion of transfusion and infusion, with extensive directions on methods. In view of the rather remarkable advances that have been made in the past year in the use of serum and plasma, it comes as a surprise to see so little space given over to a discussion of it. Some specific instructions regarding amounts of fluids, simple methods for determining patients' needs, and for establishing indications for various fluids would add greatly to the value of this chapter.

The great numbers of burns seen in the present conflict, particularly those involving the face and hands, have made this a most important topic. In view of the recent controversy regarding the use of tannic acid on hands and face, it has been somewhat surprising to see that this question is not more thoroughly discussed.

The chapter dealing with the local treatment of recent wounds emphasizes the principles of treatment and the importance of cleansing to convert a contaminated and devitalized wound into a relatively clean and viable one. The excised wound

[1] THE 1940 YEAR BOOK OF RADIOLOGY. DIAGNOSIS. Edited by Charles A. Waters, M.D., and Whitmer B. Firor, M.D. THERAPEUTICS. Edited by Ira I. Kaplan, B.Sc., M.D. Chicago: The Year Book Publishers, Inc., 1940.

[2] SURGERY OF MODERN WARFARE. By sixty-five contributors, edited by Hamilton Bailey, F.R.C.S., in two volumes. Vol. 1. Baltimore: Williams & Wilkins Company, 1941.

must be given "tissue support to prevent or control edema, and immobilization to give complete rest to the injured part." Primary closure, while often possible, should be done only when the patient can be carefully watched. More often the wound should be packed with vaseline gauze and the dressings changed very infrequently. Immobilization on splints does not seem as perfect as that in a plaster encasement, although this method "must be considered to be still on trial." Carrel-Dakin treatment is still applicable in certain types of wounds.

In the local management of infected war wounds, excision is no longer possible and active intervention is undertaken for certain definite reasons only; namely, the presence of retained purulent secretion under pressure, impending or developed gas gangrene, penetrating wounds containing débris and foreign material, and compound fractures in which the bone fragments have led to widespread disruption of tissues. The operations must be carried on with the utmost gentleness, free wide exposure obtained; accurate hemostasis secured; blood clots, foreign bodies and obviously devitalized tissue, especially muscle, excised; and free drainage secured. Here too the closed method of treatment offers the advantages of complete rest and the avoidance of interference with the wound.

Gas gangrene, uncommon during the Spanish Revolution, was frequent in France in 1914–18, and in the casualties in France in the present war. The prophylactic treatment by adequate initial surgical care is stressed and local implantation of sulfanilamide or sulfapyridine is advised. Serum is advisable, though its value is still not established. X-ray treatment is recommended.

The short chapter by Flemming on the bacteriological examination of wounds is one of the most important in the book. Especially significant is his distinction between primary and secondary infection. He brings out not only the potential sources of each type, but the wound conditions which favor growth.

Delayed primary suture of wounds is indicated in those cases in which, after cleansing and excision, some doubt still exists as to the cleanliness of the wound. Secondary suture may occasionally be accomplished after a wound has become clean, preferably between the fourteenth and twenty-first day, before fibrosis becomes too great.

The chapter by McIndoe on skin grafting emphasizes quite rightly that large surfaces should not be allowed to heal by scar tissue, but should be grafted at the earliest possible moment. In the preparation of raw surfaces, the author might stress somewhat more forcefully the use of pressure dressings, and more space could have been devoted to the technique of dressing grafts, the length of time pressure should be maintained, and other details of after care.

The chapter dealing with wounds of the thorax is clearly written, terse, practical, and well illustrated. It is pointed out that in bomb blast injuries the lung is compressed by the chest wall—not exploded by inrushing air. Many lives may be saved by immediate temporary closure of sucking wounds of the chest. Hemothorax and hemopneumothorax are best treated by aspiration and air replacement in cases which cannot be submitted to early operation. In this way may be overcome the objections to aspiration on the grounds that further lung hemorrhage is encouraged when tamponade of hemothorax is removed.

The acrimonious debate relative to the necessity of operating upon abdominal wounds with visceral damage was settled definitely in the early stages of the war of 1914–18. At the present time cases are classified into those in which patients are in good condition and operable, in collapse but capable of resuscitation, and in a dying condition and beyond aid. Time should be spent in preparing patients for operation, with fluids, warmth, and sedatives, regardless of the general condition. If active hemorrhage is present, resuscitory measures are started and operation is begun as soon as preparations are completed. The keynote of success is gentleness and timeliness of operation rather than speed. Wounds of exit and entrance are excised as in other wounds, but this is deferred until the laparotomy has been completed. A midline incision is the best all-around exposure, although the transverse incision deserves wide usage. The methods of dealing with various types of intra-abdominal lesions are given in separate chapters.

The chapter concerning the use of tourniquets is especially enlightening and the instructions and caution in their use are valuable. Interest in the immediate care of blood vessel injuries must of necessity center largely upon rapid and safe exposure for the purpose of controlling hemorrhage. Injured vessels must be exposed for a good distance above and below the site of injury, and accompanying structures, especially nerves, must be identified. Repair of blood vessel injuries is described briefly and reference is made to the use of heparin in the conservative management of vascular wounds.

Secondary hemorrhage, during 1914–18, was noted as diminishing in frequency with improvement in wound excision. Thus the prophylaxis of the condition is clearly indicated. Immediate control is best obtained by pressure rather than by tourniquet, which may further devitalize already badly devitalized tissues. In the operative control of the hemorrhage, ligation of the actually bleeding vessel is the method of choice. Proximal ligation of the vessel, except in case of gluteal hemorrhage, is not advised. Reference is made in several places to the dangers of the application of heat to badly vascularized extremities. Two chapters are devoted to the management of arterial hematomas, traumatic aneurysm, and arteriovenous aneurysm.

The chapter dealing with methods of applying traction to limbs, while adding nothing new, presents this subject in a clear, practical manner. The Thomas splint is carefully described as are also the Thomas frame, the Braun splint with its various

modifications by Boehler, and the many uses of Cramer wire.

One of the largest chapters in the book is devoted to the use of plaster-of-Paris. Careful detailed instructions are given concerning the application of plaster to all parts of the body, and a host of practical suggestions are made.

Wounds of the hand are treated on the same principles as wounds elsewhere. Primary nerve repair, where possible, is advised, but tendon suture is seldom permissible. Splinting in the position of function as advised by Kanavel is justly advocated as an essential primary principle. Many refinements of technique and methods of soft tissue repair are not mentioned, probably because in the author's opinion such care is not usually possible in wartime injuries. However, certainly in civilian air-raid casualties the opportunity must often present itself to do a really "bang-up" job on a severely injured hand with primary nerve and tendon repair and primary skin grafting.

The chapter on infected wounds of the hand conforms in general to the classical teachings of Kanavel. It is difficult for the reviewer to accept the pronouncement that the warm moist pack is being supplanted by dry heat, and still more difficult to be impressed by the rotation dressings of eusol, hydrogen peroxide, magnesium sulphate, and normal saline applied every 4 hours in rotation. Iselin's incisions for tenosynovitis with through and through drainage of the web spaces are also difficult to accept.

Wounds and infections of the foot are considered both from the standpoint of wound care in general and from the standpoint of functional requirements of the foot itself.

Two final chapters deal with knee joint and hip joint injuries.

A reading of this excellently prepared volume strengthens one in the conviction that the war surgeon must be capable of dealing intelligently with emergency surgery anywhere on the body. The medical units upon whom will fall initially the great mass of wounded must be made up of well trained, quick-acting surgeons who are firmly grounded in surgical principles. It is to men of this type that the volume will be most helpful. MICHAEL L. MASON.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

FRACTURES AND OTHER BONE AND JOINT INJURIES. By R. Watson-Jones, B.Sc., M.Ch.Orth., F.R.C.S. 2d ed. Baltimore: The Williams & Wilkins Co., 1941.

THE STORY OF CLINICAL PULMONARY TUBERCULOSIS. By Lawrason Brown, M.D. Baltimore: The Williams & Wilkins Co., 1941.

ENTRE CIRUJANOS Y HOSPITALES. By Dr. Jose Castro Villagrana. Mexico City: The Author, 1940.

ESSENTIALS OF GYNECOLOGY. By Leo Brady, M.D., F.A.C.S., and Ethna Louise Kurtz, R.N. New York: The Macmillan Co., 1941.

PROCEEDINGS OF THE FIRST AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY AT CLEVELAND, OHIO, SEPTEMBER 11–15, 1939. Fred L. Adair, A.M., M.D., F.A.C.S., Editor. Evanston, Illinois: The Mumm Print Shop, Inc., 1941.

OBSTETRICS FOR NURSES. By Joseph B. DeLee, A.M., M.D., and Mabel C. Carmon, R.N. 12th rev. ed. Philadelphia and London: W. B. Saunders Co., 1941.

BIOLOGICAL SYMPOSIA; A SERIES OF VOLUMES DEVOTED TO CURRENT SYMPOSIA IN THE FIELD OF BIOLOGY. Edited by Jaques Cattell. Vol. 3—MUSCLE. Lancaster, Pennsylvania: The Jaques Cattell Press, 1941.

ESSENTIALS OF ENDOCRINOLOGY. By Arthur Grollman, Ph.D., M.D. Philadelphia, London, and Montreal: J. B. Lippincott Co., 1941.

SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES. By George R. Herrmann, M.S., M.D., Ph.D., F.A.C.P. 2d ed. St. Louis: The C. V. Mosby Co., 1941.

LOS ABSCESOS DEL PULMON. By Dr. Ismael Cosío Villegas. Mexico: Compania General Editora, S.A., 1940.

ACCIDENTAL INJURIES; THE MEDICO-LEGAL ASPECTS OF WORKMEN'S COMPENSATION AND PUBLIC LIABILITY. By Henry H. Kessler, M.D., Ph.D., F.A.C.S. 2d ed. Philadelphia: Lea & Febiger, 9141.

THE MEDICAL ASPECT OF BOXING. By Ernst Jokl, M.D. Pretoria, South Africa: J. L. Van Schaik, Ltd., 1941.

COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Edited by Richard M. Hewitt, B.A., M.A., M.D., A. B. Nevling, M.D., Harry L. Day, Ph.B., M.D., John R. Miner, B.A., Sc.D., James R. Eckman, A.B., and M. Katharine Smith, B.A., Vol. 32. Philadelphia and London: W. B. Saunders Co., 1941.

THE MARCH OF MEDICINE; NO. 5 OF THE NEW YORK ACADEMY OF MEDICINE LECTURES TO THE LAITY, 1940. New York: Columbia University Press, 1941.

ORBITAL TUMORS; RESULTS FOLLOWING THE TRANSCRANIAL OPERATIVE ATTACK. By Walter E. Dandy. New York: Oskar Piest, 1941.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. Newman Dorland, A.M., M.D., F.A.C.S., with the collaboration of E. C. C. Miller, M.D. 19th ed. Philadelphia and London: W. B. Saunders Co., 1941.

X-RAY THERAPY OF CHRONIC ARTHRITIS (INCLUDING THE X-RAY DIAGNOSIS OF THE DISEASE); PRELIMINARY REPORT BASED ON 100 PATIENTS TREATED AT QUINCY, ILLINOIS. By Karl Goldhamer, M.D. With a Foreword by Harold Swanberg, B.S., M.D., F.A.C.P. Quincy, Illinois: Radiologic Review Publishing Co., 1941.

FIT TO FLY; A MEDICAL HANDBOOK FOR FLIERS. By Malcolm C. Grow, M.D., and Harry G. Armstrong, B.S., M.D. New York and London: D. Appleton Century Co., Inc., 1941.

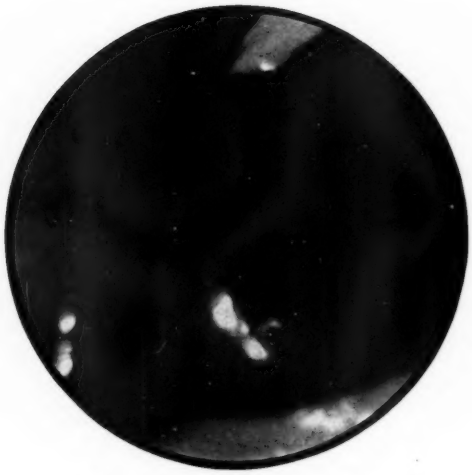


Fig. 1. Photograph of the liver in a case of uncontrolled diabetes mellitus, taken with an endoscopic camera. The tip of each lobe is high-lighted.

Intra-Abdominal Photography in Color.—Thomas N. Horan and C. Graham Eddy.

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